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VOLUME 48 NUMBER 3

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SEPTEMBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

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Archives of Internal Medicine

VOLUME 48 SEPTEMBER, 1931 NUMBER 3

EXOPHTHALMIC GOITER

THE DEVELOPMENT OF REFRACTORINESS TO IODINE *

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AND
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Soon after the treatment for exophthalmic goiter with iodine became general, it was recognized that during prolonged administration the basal metabolism often rose markedly after an initial drop, in association with an increase in the severity of the disease. Nevertheless, the impression has prevailed that as long as iodine is being given in excess the peculiar nervous manifestations of exophthalmic goiter are completely under control, regardless of what happens to the rate of the basal metabolism.[1] Certain observations that we have made suggest that this may not always be the case.

During the continuous administration of iodine in the following case, the patient, after initially showing a marked response to the administration of about 6 mg. (1 drop of the compound solution[2])

* Submitted for publication, Dec. 23, 1930.

* From the Thyroid Clinic and Metabolism Laboratory, Massachusetts General Hospital, Boston, the Department of Medicine, Rush Medical College and the Presbyterian Hospital, Chicago.

1. This appears to be largely the result of a rather general acceptance of Plummer's ingenious hypothesis. Plummer said: "Lugol's solution controls only the abnormal product. . . . We have not seen that phase of the exophthalmic goiter picture which we attribute to the abnormal product become more marked while the patient was on Lugol's solution. Theory and experience seem to indicate that the amount of the normal product sometimes increases when the patient is taking iodine" (Plummer, H. S., in discussion of Mason, E. H.: Iodine Therapy in Toxic Goitre, Tr. A. Am. Physicians **39**:167, 1924). Elsewhere he said: "Is the control of that part of the complex attributed to an abnormal product absolute? In other words, will the administration of Lugol's solution in cases of exophthalmic goiter in amounts somewhere between 10 and 40 minims daily from the inception of the disease ever be followed by the characteristic complex even though hyperthyroidism becomes intense? That the evidence warrants seriously considering an affirmative answer is significant" (Mayo, C. H., and Plummer, H. S.: The Thyroid Gland, St. Louis, C. V. Mosby Company, 1926, part 2, p. 77).

2. We have previously shown that this is roughly the minimum dose of iodine that will produce a maximum reduction in the rate of basal metabolism in most cases of exophthalmic goiter that occur in Boston (Thompson, W. O.; Brailey, A. G., and Thompson, P. K.: The Effective Range of Iodine Dosage in Exophthalmic Goiter: Preliminary Report, J. A. M. A. **91**:1719 (Dec. 1) 1928. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:261 [Feb.] 1930).

daily, slowly became completely refractory to this dose, both from the standpoint of basal metabolism and from that of signs and symptoms. Exophthalmos first appeared as refractoriness developed.

REPORT OF CASES

CASE 1.—The patient, Miss A. P. Y.[3] (chart 1), an unmarried Nova Scotian girl, aged 21, entered the Massachusetts General Hospital, on June 15, 1927, with a slightly atypical case of exophthalmic goiter. There were no ocular signs, and the intelligence was perhaps slightly below the average. In spite of this, however, the patient was unusually cooperative. It was decided by the medical service concerned to determine the accuracy of the diagnosis by various manipulations of iodine therapy before proceeding with surgical intervention. The only basal metabolism test performed before the beginning of iodine therapy was done in the outpatient department on June 7, and gave a result of +69 per cent. During rest in bed and the administration of compound solution of iodine, the metabolic rate dropped to +11 per cent. The patient was discharged and iodine was omitted. Within eight days the rate of metabolism had risen to +73 per cent and most of the characteristic signs and symptoms of exophthalmic goiter were present, except exophthalmos. Compound solution of iodine was again given in a dose of 1 drop daily, and within eight days the metabolism dropped to +27 per cent, and there was a striking clinical improvement. Shortly afterward the dose was increased to 15 drops daily, and finally to 30 drops daily. It seems that on the administration of 30 drops the rate of metabolism dropped temporarily to a lower level than on the administration of 1 drop daily, although it quickly rose again to the former level. After a total period of twenty-three days, the large doses were discontinued, and a dose of 1 drop was again employed daily. On the administration of this dose the rate of metabolism slowly rose, and a gradual increase in the severity of the clinical signs and symptoms was associated with this rise. Sixty-two days after this dose was started again, the rate was about +55 per cent. At this point the dose was increased to 30 drops daily. Within six days the rate dropped to about +35 per cent, and at the same time a slight clinical improvement associated with a gain in weight took place. At the end of ten days the dose was increased to 90 drops daily and, during a period of one week, this did not produce significant further reduction in the metabolic rate or further clinical improvement. A dose of 1 drop daily was then resumed, and the metabolism rose from a level of +33 per cent on November 4 to a level of +80 per cent on December 1. As the metabolic rate was thus rising, all of the signs and symptoms of the disease, including the emotional instability, slowly became more intense, and by December 1 the disease was more severe than it had been previously. Nervousness and irritability were marked. The patient perspired profusely. There was pronounced flushing of the skin, and the patient wept on slight provocation. Two months before this, the

3. Part of the data in cases 1 and 2 have been recorded elsewhere to illustrate other points (Thompson, Brailey, Thompson and Thorp [footnote 2, second reference]. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, Arch. Int. Med. **45**:481 [April] 1930).

eyes first began to be somewhat prominent. Iodine was omitted on December 1, and no significant change was noted either in the disease itself or in the metabolism until Jan. 24, 1928, when a spontaneous reduction had occurred associated with a slight decrease in the severity of the disease. On February 3, the administration of compound solution of iodine was started again in a dose of 1 drop daily. By February 9 the rate of basal metabolism had dropped from +65 per cent to a level of about +35 per cent. There was no further reduction in the metabolic rate when the dose was increased to 10 drops daily. Shortly afterward the patient was admitted to the hospital, where, in association with rest in bed, the rate of metabolism dropped to a level of about +20 per cent. A subtotal thyroidectomy was performed on February 28 and was followed by an uneventful convalescence.

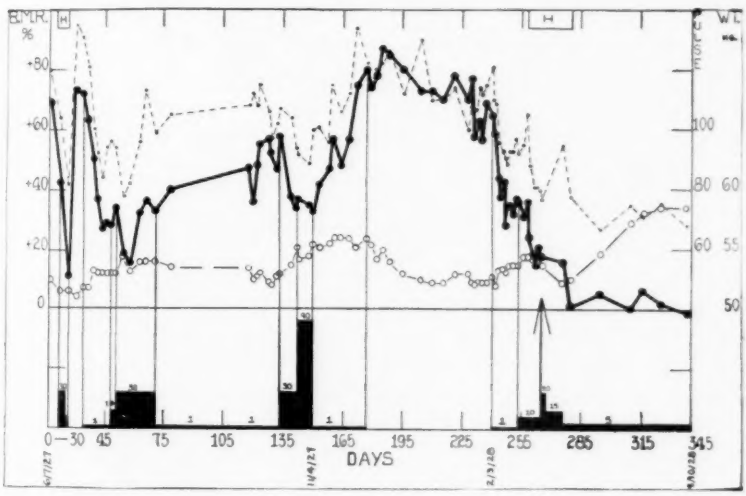

Chart 1 (case 1).—The development of complete refractoriness to 1 drop of compound solution of iodine daily during its prolonged administration to a patient with exophthalmic goiter. Its development was preceded by a well marked response to this dose and was followed by a well marked response to it after a period of omission of iodine. The initial short period of iodinization did not appear to be associated with the development of refractoriness, whereas the prolonged administration was. In this and subsequent charts, black areas denote periods of treatment with compound solution of iodine, and the figures above them, the daily doses in drops; arrows, subtotal thyroidectomies; half arrows, hemithyroidectomies; *H*, a period of hospitalization. The black line indicates the basal metabolic rate; the circle line, the weight in kilograms, and the dash line, the pulse rate.

The following case is similar to the first in that, during the continuous administration of iodine, the patient showed an initial improvement, and then a gradual increase in the intensity of all of the signs

and symptoms, including the peculiar nervous manifestations. The eyes first began to increase in size as the basal metabolic rate rose during the administration of iodine. Unlike the first case, however, the condition became only partially instead of completely refractory to small doses (about 6 mg. of iodine administered daily).

CASE 2.—The patient, Mrs. E. H.[3] (chart 2), a married woman, aged 26, first came to the metabolism laboratory of the Massachusetts General Hospital on Oct. 10, 1927, complaining chiefly of dyspnea. The rate of basal metabolism at that time was + 22 per cent. The catamenia had begun to be scanty; she had diarrhea and had lost 33 pounds (15 Kg.). There were no ocular signs. The thyroid gland was firm and symmetrically and moderately enlarged with a soft

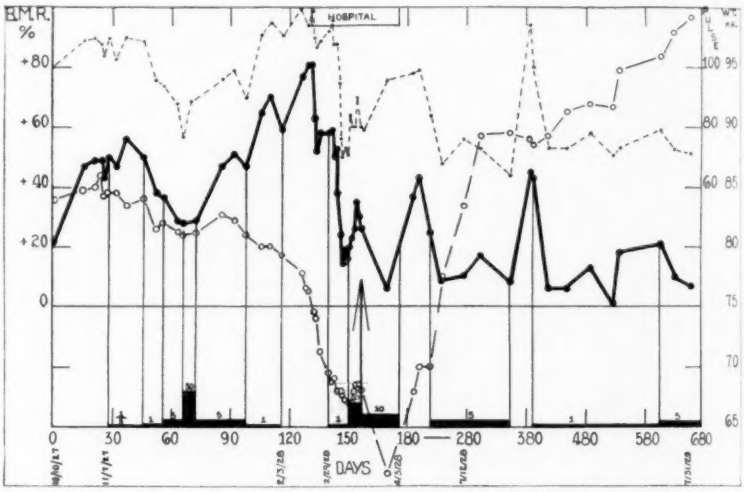

Chart 2 (case 2).—The development of partial refractoriness to 1 drop of compound solution of iodine daily during prolonged administration, and recovery from this refractoriness on the omission of iodine.

systolic bruit all over, most marked at the superior poles. There was a fine tremor, and the skin was warm and moist. The onset of the disease had apparently occurred eleven months previously, and the goiter had been noticed six months before the patient came to the hospital. It was decided to give iodine as a therapeutic test. While a metabolic level was being secured, the rate of basal metabolism rose to about + 50 per cent. It remained at this level from October 26 until November 7, when the administration of compound solution of iodine was started in a dose of 1 drop of a 20 per cent solution daily. This produced no change, except, perhaps, to make the thyroid gland slightly larger and firmer. On November 25, the dose was increased to 1 drop of the undiluted solution daily. While this dose was being administered, the rate of metabolism dropped to +37 per cent, and the patient felt less nervous and tired less easily. On December 5, the dose of iodine was increased to 5 drops daily. On the administration of this

dose the improvement was more marked, and the rate of metabolism dropped to + 28 per cent. On December 15, the dose was increased to 20 drops daily. This did not produce a further reduction in the rate of basal metabolism or further clinical improvement. The thyroid was much firmer and somewhat larger during the administration of 30 drops daily than before the iodine therapy was begun, and the bruit had become less marked. On December 22, the dose of iodine was reduced to 5 drops daily. On this dose the rate of basal metabolism rose to a level of +48 per cent. The patient was more irritable, had more palpitation and complained of frontal headaches. There was no reduction in the size or firmness of the thyroid, over which there was a faint bruit. The latter was much less marked than before the use of iodine, although the rate of metabolism was the same. On Jan. 16, 1928, the dose of compound solution of iodine was reduced to 1 drop daily. On this dose the rate of metabolism promptly rose to about + 65 per cent, and the patient was more nervous, slept more poorly, had more frequent crying spells and more palpitation, fatigued more easily and perspired more profusely. She had a marked tremor. The thyroid continued to be very firm, but seemed slightly softer than it had been during the administration of 30 and 5 drops daily. There was a faint bruit at the right superior pole. For the first time, the eyes began to smart and water and to cause pain when she read. They appeared somewhat full, but there was no definite lid lag. At about this time the family began to notice that the eyes were more prominent than they had been. On February 3 iodine was omitted, and the patient became still worse. She had still more palpitation and dyspnea on the slightest exertion, and the diarrhea returned. The thyroid continued to be firm for some time. She was admitted to the hospital on February 17. On February 18, it was noted that the right eye was larger than the left, and that there was a bilateral lid lag. The patient was more ill than at any time since she had been under observation. She thrashed about in bed. She was emotionally unstable, extremely short of breath and perspired profusely. She appeared washed out. The goiter was even harder and firmer than before the administration of iodine was begun. However, by February 23, it was noted that the thyroid was much softer than on admission. By February 25 she had vomited several times. The marked toxicity during this period was reflected in the rapid loss of weight. With only rest in bed, the rate of metabolism dropped from + 81 to + 58 per cent. On February 29, the administration of compound solution of iodine was started in a dose of 1 drop daily. By March 6 the rate of the metabolism had dropped to about + 16 per cent. The vomiting had stopped; the patient was much quieter, and the thyroid had again become firmer, although a soft systolic bruit persisted, which was more marked on the right than on the left. On March 8, the dose was increased to 30 drops daily, but this produced no further reduction in the rate of basal metabolism; in fact the rate rose slightly on this dose. A subtotal thyroidectomy was performed on March 15, 1928. The immediate convalescence was somewhat delayed by a pulmonary infection, but otherwise was uneventful. Although the thyroidectomy was extensive, within about one month afterward, the basal metabolic rate rose to + 37 per cent, and the thyroid tissue had begun to regenerate. However, up to the time we left Boston it had been possible to hold this persistent thyrotoxicosis in check by the administration of iodine.

The following case is similar to the preceding one in that the condition became partially and not completely refractory to treatment with iodine (5 drops of the compound solution daily). Exophthalmos increased as the rate of metabolism rose during the administration of iodine.

Case 3.—The patient, Mrs. E. R.[4] (chart 3), a married woman, aged 34, was admitted to the outpatient department of the Massachusetts General Hospital on Dec. 27, 1928, with a typical case of exophthalmic goiter. There was well marked exophthalmos, lid lag, tremor and marked emotional and vasomotor instability (particularly for the preceding six months). For three years the thyroid gland had been diffusely enlarged, and there was a bruit over it. During the administration of 1 drop of compound solution of iodine daily the rate of the basal metabolism dropped from a level of + 45 per cent on Jan. 15, 1929, to + 19 per cent on January 22, and a marked clinical improvement was noted. Slight reduction in exophthalmos had occurred by February 12. The thyroid gland, which was soft before the administration of iodine, became hard and firm. The administration of

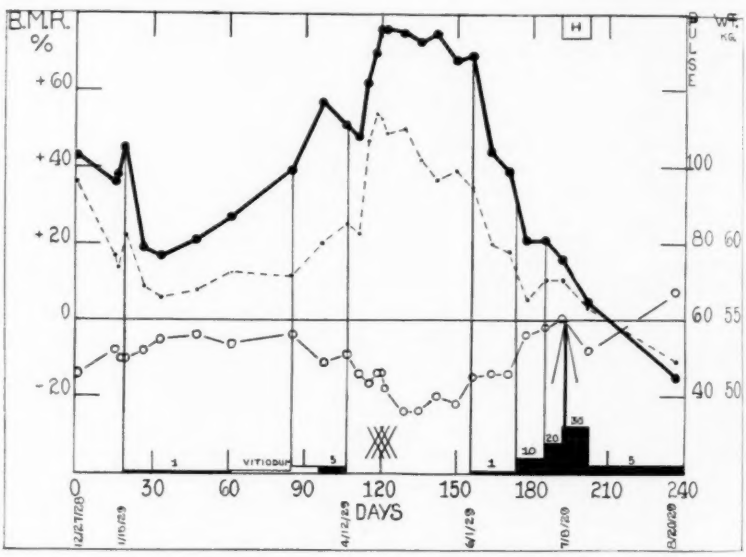

Chart 3 (case 3).—The development of partial refractoriness to 5 drops of compound solution of iodine daily during the prolonged administration of iodine, and recovery from this refractoriness on the omission of iodine. *X* denotes roentgen treatment.

iodine was continued, and by about February 26 the rate of basal metabolism had begun to rise. Increasing the dose of iodine about one month later to 5 drops of the compound solution daily did not appear to prevent a further rise. By March 21, when the basal metabolism was + 39 per cent, the patient was more nervous and irritable than she had been, but not as much so as before treatment with iodine was begun. By April 2, 1929, the rate of basal metabolism had risen to + 57 per cent and the patient was much worse. She was unable to sit

4. Part of the data on this patient has been recorded elsewhere to illustrate another point (Thompson, Thompson, Brailey and Cohen [footnote 3, second reference]).

still; she was more nervous; she perspired more profusely, and she was more emotionally unstable than she had been previously. The right eye had again increased in size. Most of the time she was depressed, frightened and very suspicious. The thyroid gland had become very hard. Having already had experience with such cases, we decided to omit treatment with iodine for a period before proceeding with surgical intervention. This was done on April 12, and the rate of metabolism rose about 20 points during the next thirteen days to a level of about + 75 per cent, and the disease became still more severe. The thyroid gland slowly became softer again. The subsequent course of the disease was complicated by the fact that the patient was given three roentgen treatments (at her request), which were followed by a slight clinical improvement but no significant change in the basal metabolic rate. After an interval of fifty days, iodine was readministered, first in a dose of 1 drop of the compound solution daily and then in a dose of 10 drops daily. This produced a reduction in the rate of basal metabolism from + 69 per cent to + 21 per cent and an improvement in the disease. A subtotal thyroidectomy, performed shortly afterward, was followed by only a slight reaction, and the patient made an uneventful recovery.

The following patient, who had a severe case of exophthalmic goiter, was apparently refractory to iodine (250 mg. daily) on admission to the hospital, after taking the compound solution continuously for one month. Owing to a rapid pulse rate at the time of the first appearance in the operating room, the surgeon did only a bilateral ligation of the superior thyroid arteries. A subtotal thyroidectomy was performed about eleven weeks later. Each operation was preceded by a period of omission of iodine therapy. Judging by the uneventful convalescence from each operation and from the course of the basal metabolism, it is probable that a subtotal thyroidectomy could have been done the first time the patient was taken to the operating room, although at the time the alternative decision seemed wiser.

Case 4.—The patient, Mrs. A. A. (chart 4), a married woman, aged 23, was admitted to the Woodyatt service of the Presbyterian Hospital on March 17, 1930, complaining of nervousness of three years' duration and of fatigability, profuse perspiration, generalized itching, loss of weight, increased appetite, weakness, increased thirst, polyuria, palpitation, irritability and scantiness of menstruation of three months' duration. The patient was restless and constantly moved about. Loud laughter alternated with profuse weeping. There was a well marked tremor of the extended fingers. There was puffiness of the upper and lower eyelids and a stare, but no lid lag. The thyroid was hard and firm, and there was no bruit over it. At the time of admission, the patient had been given 30 drops of compound solution of iodine daily for about a month, and the metabolic rate was + 110 per cent. Feeling that this indicated that the condition was refractory to iodine, this medicine was omitted on the day of admission. In spite of this, the rate of basal metabolism dropped to a level of about + 80 per cent, except for a slight temporary rise associated with menstruation (the only menstrual period while the patient was in the hospital). By March 24 the thyroid had become fairly soft, and by March 31 it had become still softer and had decreased to half its previous size. A systolic bruit was present all over, most marked at the superior poles. There was no increase in the emotional instability and no increase in the size of

the eyes. On March 31 the administration of compound solution of iodine was started in a dose of 10 minims (0.6 cc.) three times daily. The rate of basal metabolism dropped to a level of about + 55 per cent by April 7. After the administration of iodine the thyroid again began to increase in size. By April 4 it was nearly twice its size on March 31, but it did not become hard until April 10. In association with the drop in metabolism, the signs and symptoms of the disease decreased, but they did not disappear, as shown by the following note of April 11: "All the symptoms of the disease persist in a somewhat subdued form and the patient should be operated on either at once or after a more prolonged period of omission of iodine. She is by no means the best operative risk, but will not become better so long as iodine is continued." The patient was taken to a surgical clinic for operation on the morning of April 14. While waiting for the anesthesia to be started, she became somewhat nervous and the pulse rate rose to 176. It did not quiet down under ethylene so Dr. Bevan performed only a

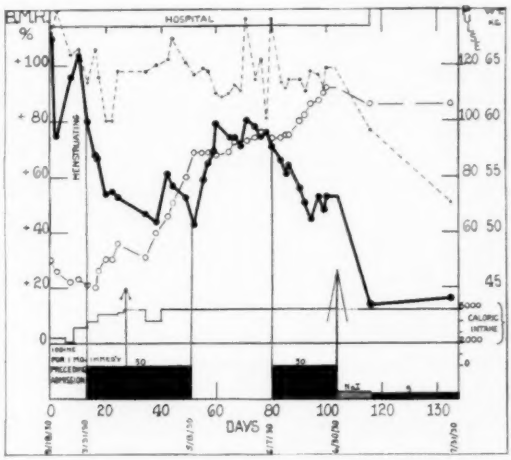

Chart 4 (case 4).—A patient in whom the condition was apparently completely refractory to the administration of 30 drops of compound solution of iodine daily on admission to the hospital after having taken this dose for one month. Partial recovery from refractoriness during a short period of omission of iodine. The small arrow denotes bilateral ligation of the superior thyroid arteries.

bilateral ligation of the superior thyroid arteries and removed an enlarged cervical lymph gland, which was reported to be normal. The postoperative convalescence was uneventful. Following operation the rate of basal metabolism did not change appreciably until after iodine was omitted on May 8. It then rose within fourteen days to a level of from + 70 to + 80 per cent, accompanied by a decrease in the size and firmness of the thyroid gland and (by May 15) an increase in perspiration, nervousness, emotional instability and the other signs and symptoms of the disease, except exophthalmos. Compound solution of iodine was readministered on June 6, 1930, in a dose of 10 minims three times daily. On the administration of this dose, the rate of the metabolism dropped to a level of about + 50 per cent by June 18, and the patient felt much better than during the preceding

administration of iodine, in spite of the fact that the rate of metabolism was not significantly lower. A subtotal thyroidectomy was performed by Dr. Bevan on June 30, and was followed by an uneventful convalescence. The highest postoperative temperature was 101.5 F., and vomiting had ceased within twenty hours.

The gain in weight of 40 pounds (18.1 Kg.) preceding thyroidectomy, part of which occurred during the second period of the omission of treatment with iodine was the result of the excessive caloric intake (about 5,000 calories most of the time). The excellent physical condition of the patient thus produced, may have been a factor in the uneventful convalescence, as the rate of basal metabolism was as low before the second omission of treatment with iodine as after it was readministered.

Pathologically, the thyroid gland showed changes characteristic of exophthalmic goiter.

Unlike the four preceding cases, operation was performed in the following case when the rate of metabolism was rising rapidly during the administration of iodine. The patient's death from a typical thyroid crisis about forty hours later stands out in striking contrast to the uneventful recoveries in the other cases and illustrates the danger of operation at such a time. This case was similar to the first three cases in that the peculiar nervous manifestations of exophthalmic goiter, including exophthalmos, became worse as the rate of metabolism rose during the administration of iodine. It differed from the other cases in that this rise occurred much sooner after the initial improvement, during the administration of much larger doses of iodine, and was much more rapid, and in that the patient had acute rheumatic fever as well as exophthalmic goiter.

Case 5.—The patient, Mr. H. E. B.[5] (chart 5), an American laborer, aged 20, single, entered the Massachusetts General Hospital on June 12, 1929, with a typical case of exophthalmic goiter of about seven months' duration. The case was complicated by acute rheumatic fever that had started one week before admission. In spite of the presence of this acute inflammation, he drove by motor car from his home to the hospital, a distance of 112 miles. On admission the patient was nervous and feverish, and his skin was warm and moist. He had marked exophthalmos, a bilateral lid lag and poor convergence. The thyroid gland showed a well marked symmetrical enlargement with a thrill and a marked bruit over it. There was a marked tremor of the fingers. The heart was enlarged to the left, and there was a presystolic thrill and a rough systolic murmur at the apex and an accentuated pulmonary second sound. The right shoulder and left knee were painful on motion, and the left ankle was swollen, warm and tender. The day after admission there was a to-and-fro frictional rub over the base of the heart, muffled sounds at the apex and well marked enlargement. The administration of

5. It was decided that this case should be reported in the "Case Records of the Massachusetts General Hospital" from the standpoint of the combination of rheumatic fever and exophthalmic goiter in the same patient (Mallory, T. B.; Means, J. H., and Young, E. L.: Exophthalmic Goiter and Acute Rheumatic Fever, Case no. 15472, New England J. Med. **201**:1056, 1929), and that we should report it from the standpoint of refractoriness.

salicylates was begun on the day of admission, and the next day the administration of a compound solution of iodine was started and continued daily thereafter in large doses. The exophthalmic goiter and the rheumatic fever slowly improved, and the temperature dropped from 103.3 F. on admission to normal by June 18 and remained practically normal until after operation. Owing to the serious condition of the patient, no attempt was made to determine the metabolic rate until he had improved. The first basal metabolic rate of + 40 per cent obtained on June 21,

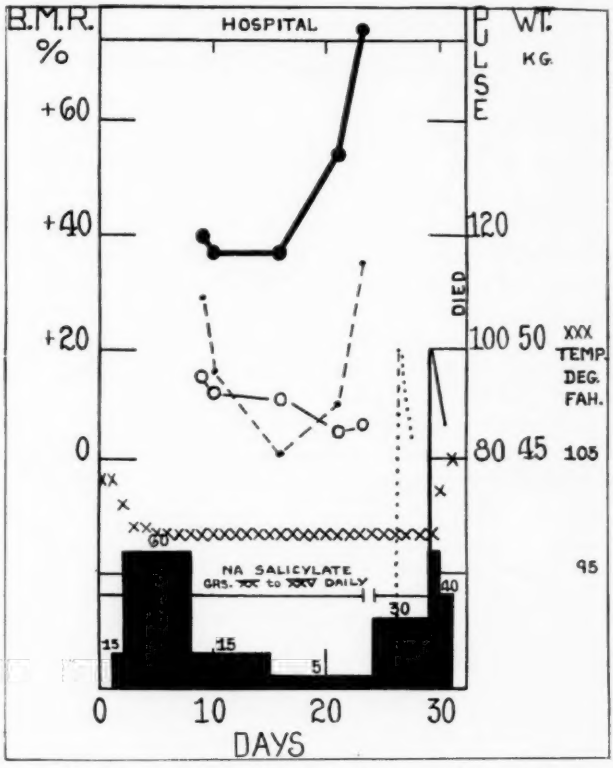

Chart 5 (case 5).—Rapid development of refractoriness to 30 minims of compound solution of iodine administered daily following a short period of improvement. A hemithyroidectomy performed during the period of rising metabolism was followed by a typical thyroid crisis and death in forty hours. Dotted arrow denotes attempt at operation.

therefore represents the level to which iodine reduced it, and judging from the clinical improvement during the administration of iodine the rate of basal metabolism on admission was probably much higher. The metabolism remained at this level until June 28, and, during this time, the clinical improvement in the patient was striking, although the weight decreased slightly. Unfortunately, it was felt

that the patient should not be operated on until sodium salicylate had been omitted long enough to see whether the rheumatic fever was still active. This was not done until July 5. In the meantime, the basal metabolic rate had risen by July 3 to + 54 per cent, and there was an exaggeration of symptoms; i. e., he was more nervous and restless and had a wilder look in his eyes. By July 5, the rate of metabolism had risen still further to + 76 per cent, and the signs and symptoms of exophthalmic goiter were still more exaggerated. It was decided that operation should be performed at once, and the administration of sodium salicylate accordingly was started again on July 6 after having been omitted for only twenty-four hours. On July 7 the patient was prepared for operation in the usual manner, but on arrival in the operating room the condition was so serious that operation was postponed. The pulse rate was 180 +, and the patient was extremely nervous and tossed about incessantly. He stated that he was not especially worried about the operation and that he was unable to account for his nervousness. He was kept as quiet as possible, and operation was again attempted on July 11. A right hemithyroidectomy was performed in thirty-five minutes. It was thought that he stood the operation fairly well, and his condition was said to be reasonably satisfactory when he returned to the ward. A few hours after operation, however, the temperature was 102 F. by mouth and later 103 F. by rectum. That night it was 105.3 F. by rectum, and it remained at about this level until he died at 12.01 a. m., on July 13. The pulse rate corresponded with the temperature, and after he returned from the operating room it slowly rose from 100 to 153. The next morning it was from 120 to 140 and slowly rose until it was over 200 shortly before death. Following operation he became extremely nervous; he perspired profusely, and he was cyanotic and thrashed about in bed. Putting the patient in an oxygen tent reduced the cyanosis slightly. A few hours before death he became irrational. Compound solution of iodine was given in large quantities by rectal taps after operation; physiologic solution of sodium chloride was given intravenously, by rectum and subpectorally, and dextrose was given intravenously and by rectum. The patient also took a considerable quantity of water and some iodine by mouth.

The mass of thyroid tissue removed at operation weighed 104.5 Gm. and on microscopic examination the acini showed "considerable variation in size, the majority being large but only partially distended with colloid." They were "lined by high columnar epithelium showing numerous papillary projections." At autopsy, the thymus weighed 28 Gm., the mesenteric lymph glands and the spleen were slightly enlarged, and the heart showed a healing fibrinous pericarditis, slight fibrous thickening and numerous small translucent granules about the edges of the mitral valve. The lungs showed passive congestion, but evidence of pneumonia was not present.

In this patient, as in the preceding four, the thyroid gland became much firmer when iodine was administered than it was before, and, as in the first three cases, this firmness persisted when the rate of basal metabolism rose during the administration of iodine.

It might be argued that in this patient the basal metabolic rate began to rise only when the dose of the compound solution was reduced from 15 minims (0.9 cc.) daily to 5 minims (0.3 cc.) daily. Because of the small dose of iodine that will produce a maximum effect in exophthalmic goiter,[2] it seems unlikely that this reduction was responsible for the increase in the rate of basal metabolism. Moreover, the

patient received 30 minims (1.8 cc.) daily for five days just before operation, without clinical improvement, and larger doses immediately after operation.

The following data are recorded to illustrate that a patient who shows little or no reduction in the rate of basal metabolism during the administration of iodine may improve clinically (prolonged rest presumably being a factor) and have a fairly satisfactory convalescence

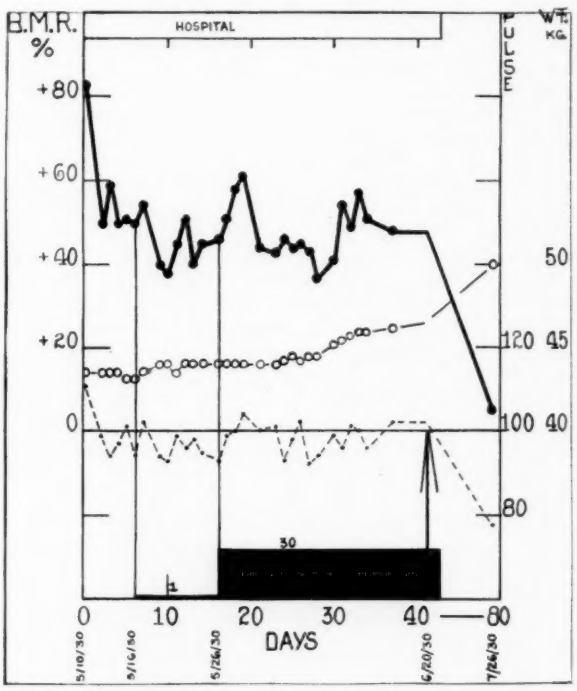

Chart 6 (case 6).—Definite clinical improvement but no reduction in the basal metabolic rate during rest and the administration of iodine in large doses. Subtotal thyroidectomy was followed by only moderate postoperative reaction.

from a subtotal thyroidectomy. A few other patients who responded similarly have been observed.

From the standpoint of operative risk, it would appear that a moderately high stationary rate of metabolism during the administration of iodine may be a less serious omen than a rapidly rising rate of metabolism during the administration of iodine.

Case 6.—The patient, Mr. W. N. (chart 6), an American painter, aged 36, entered the Brown service of the Presbyterian Hospital, on May 9, 1930, with a

typical case of exophthalmic goiter of about four months' duration. On admission he was very nervous, restless and emotionally unstable. The skin was warm, moist and somewhat flushed. There was a well marked fine tremor of the extended fingers, well marked bilateral exophthalmos and lid lag, poor convergence and a moderate symmetrical enlargement of the thyroid gland with a systolic bruit all over the right lobe, which was most marked at the superior pole. The day after admission the basal metabolic rate was + 83 per cent, but during the test the patient was restless, and this result probably did not represent the true basal metabolic level at that time. Two days later it was + 50 per cent, and it remained at approximately this level until after operation. The patient had been using iodized salt for domestic purposes for several years, but he had not had iodine in any other form before admission. The administration of iodine was started on May 16 in a dose of about 6 mg. daily, and on May 26 this was increased to about 250 mg. daily. During rest in bed and the administration of iodine, the patient became less nervous, perspired less, slept better and suffered less from palpitation in spite of no reduction in the rate of basal metabolism. That the improvement was not so marked as it might have been, however, is shown by the following note of June 6: "Still nervous and somewhat erratic. Slight tremor. Exophthalmos persists. Bruit at right inferior pole of thyroid but not elsewhere. Thyroid hard. Well marked palpitation. Perspires freely on warm days. Sleeps well. Little worry. Says he feels '100 per cent better' than on admission. He is, however, still definitely thyrotoxic and by no means the best operative risk. It is questionable whether he should be operated on now or after a period of omission of iodine." Nevertheless, following a subtotal thyroidectomy by Dr. E. M. Miller on June 20, the patient had a satisfactory convalescence. He had the usual amount of fever for five days after operation, the highest point reached being 102 F., and there was a period of auricular fibrillation of a few hours' duration, beginning the day after operation. There was no nausea or vomiting.

PHENOMENA THAT MAY BE RELATED TO REFRACTORINESS TO IODINE

In addition to temporary improvement during the continuous administration of iodine, the following types of reaction have been observed:

1. When iodine is omitted after producing its usual remission, the rate of metabolism may quickly rise to a higher level than that noted before the administration was started (chart 7 in this article and chart 5 and the case of Mr. L. O. in Starr's [6] paper).

2. The rise following the omission of iodine may occur abruptly, even when iodine has not produced a reduction in the rate of basal metabolism (chart 8 in this article and charts 7, 8, 9 and 10 in the paper of Starr, Segall and Means [7]).

3. While iodine is being administered, the rate of metabolism may not show an initial reduction, but may rise higher than it was before

6. Starr, P.: The Course of Hyperthyroidism Under Iodine Medication, Arch. Int. Med. **39**:520 (April) 1927.

7. Starr, P.; Segall, H. N., and Means, J. H.: The Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.

the administration of iodine was started and higher still when iodine is omitted (chart 9).

4. A dose of iodine which in itself is too small to cause a reduction in the rate of basal metabolism may interfere with the effect of much larger doses administered immediately afterward.[8]

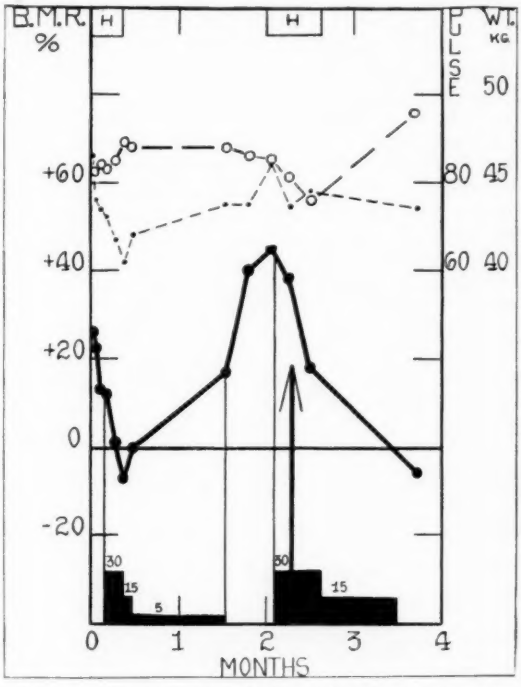

Chart 7 (Mrs. A. H., lab. no. 5917).—Omission of iodine after the usual remission (first administration) followed by a rise of the basal metabolic rate to a higher level, and greater severity of the disease than had been present initially. (The data recorded in charts 7, 8 and 9 are from the Massachusetts General Hospital.

8. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:420 (March) 1930. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, Arch. Int. Med. **45**:430 (March) 1930.

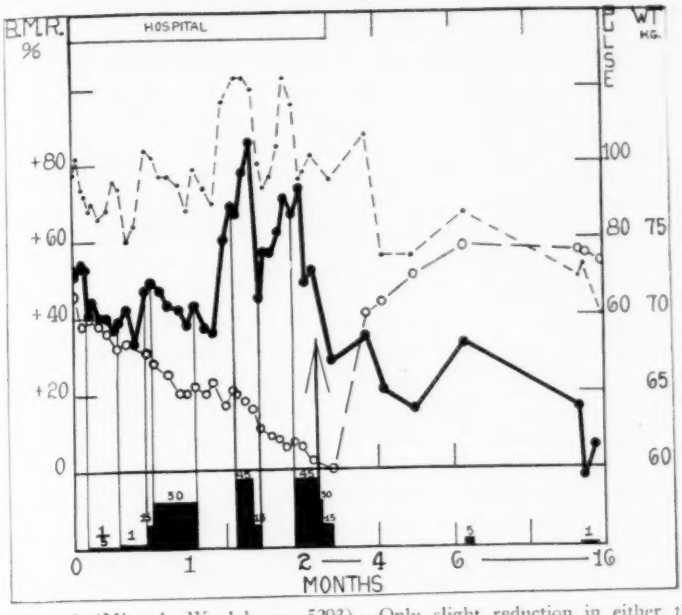

Chart 8 (Miss A. W., lab. no. 5203).—Only slight reduction in either the basal metabolic rate or the severity of the disease during the administration of iodine (first administration), followed by a well marked increase in both factors when it was omitted.

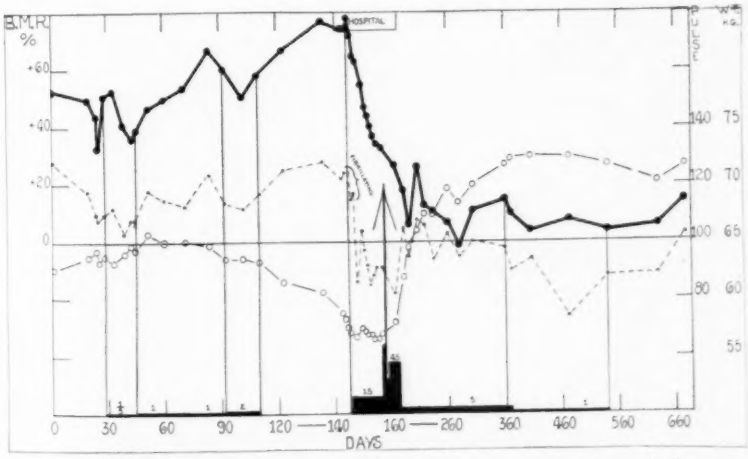

Chart 9 (Miss M. K., lab. no. 5181).—Increase in the basal metabolic rate and severity of the disease during the daily administration of one drop of compound solution of iodine, with still further increase in both factors on the omission of iodine.

It is not known in what percentage of cases each of the types of reaction previously described occurs. In the first three, the fact that the rate of metabolism was higher and the intensity of the disease greater following the omission of iodine than they were initially, is analogous to the "postiodine" reaction of Starr (chart 1 in his paper [9]). In the rare instances in which it was possible to make such observations, it was found that this increase in the intensity of the disease following the omission of iodine has usually been of only temporary duration, and has been followed by some spontaneous decrease.[9]

In this connection it is of interest that cases [10] have been reported in which thyrotoxicosis developed during the administration of iodine, although it has never been definitely proved that iodine was the cause of these flare-ups. Occasionally we have seen an increase in the rate of basal metabolism and in the severity of the disease in patients with exophthalmic goiter during the administration of from about 1.5 to 3 mg. of iodine daily, which was followed by a reduction shortly after the dose was increased to 250 mg. daily.[3] In these cases the level to which the large dose depressed the metabolism was, on the average, only slightly lower than the level just before the small doses were started. There may be some truth in the impression of older observers that iodine may aggravate cases of exophthalmic goiter and that latent cases may be lighted up through its use.

TIME REQUIRED FOR DEVELOPMENT OF AND RECOVERY FROM REFRACTORINESS TO IODINE

In case 5, iodine was not omitted, so that it is unknown whether or not the condition was completely or only partially refractory to it. While in case 1 the condition became completely refractory to 1 drop

9. Starr (footnote 6). Goetsch, E.: The Use and Misuse of Iodine in the Treatment of Toxic Goiter, New York State J. Med. **27**:1075, 1927.

10. Kocher, T.: Ueber Jodbasedow, Verhandl. d. deutsch. Gesellsch. f. Chir. **39**:396, 1910; Ueber Jodbasedow, Arch. f. klin. Chir. **92**:1166, 1910; Discussion on the Surgical Treatment of Graves' Disease, Brit. M. J. **2**:931, 1910. Fleischmann, P.: Zur Frage der regionär verschiedenen Empfindlichkeit gegen Jod, München. med Wchnschr. **58**:198, 1911. Trousseau, A.: Lectures on Clinical Medicine, translated by P. V. Bazire, The New Sydenham Society, London, lecture 19, vol 1, 1868. Sudeck: Die Jodbehandlung der Schilddrüsenerkrankungen, Klin. Wchnschr. **2**:1122, 1923. Pineles, F.: Ueber die Empfindlichkeit des Kropfes gegen Jod, Wien. klin. Wchnschr. **23**:353, 1910. Jackson, A. S.: Iodin Hyperthyroidism; Conclusions Based on a Study of Thirty-Eight Cases, Am. J. M. Sc. **170**:271, 1925. Kimball, O. P.: Induced Hyperthyroidism, J. A. M. A. **85**:1709 (Nov. 28) 1925. Hartsock, C. L.: Iodized Salt in the Prevention of Goiter: Is It a Safe Measure for General Use? J. A. M. A. **86**:1334 (May 1) 1926. Lahey, F. H.: Review of Another Year's Work in Thyroid Disease, Endocrinology **8**:366, 1924.

and in cases 2 and 3 only partially refractory to 1 drop and 5 drops, respectively, it must be emphasized that iodine was administered continuously for one hundred and forty-three days in the first case and for only eighty-eight and eighty-seven days, respectively, in the other two. The length of time that elapsed from the beginning of the administration of iodine until the rate of basal metabolism began to rise was not strikingly different in the three cases (from forty-two to fifty-eight days). The rate at which the rise occurred was slightly faster in the last two cases (1 point a day) than in the first case (one-half point a day). A marked difference is noted, however, when these three cases are compared with case 5, in which the rise in the rate of basal metabolism began at least within twenty-one days after the administration of iodine was started, and was very rapid. Owing to the rapidity of the rise and to the rather small number of observations on the basal metabolism, the rate at which it rose can only be approximated, but it could not have taken longer than eight days (from June 28 to July 5) for the basal metabolic rate to rise from + 37 per cent to + 76 per cent (39 points). Therefore, it rose at least 5 points a day. The patient had a more severe case of the disease than the other three patients.

In cases 1, 2 and 3, recovery from the refractoriness appeared to be complete after iodine was omitted. At least, in the first and third cases, when the administration of iodine was resumed, the metabolism dropped to as low a level as it had previously done when iodine had been given. The exact length of time required for this recovery is unknown, but it occurred within sixty-four, twenty-four and fifty days respectively in these three patients. The recovery in the third case was complicated by roentgen treatment. In the first case, following the omission of iodine there was some reduction in the basal metabolism and a decrease in the intensity of the disease. In the second case, there was at first a rise in the rate following the omission of iodine and then a reduction which was apparently a result of the change from the daily routine at home to rest in bed in the hospital. In case 4 the rate of metabolism during the readministration of iodine dropped to as low a level after the omission of iodine for fourteen days as after its omission for twenty-nine days.

After the omission of iodine for twenty-seven days in the case summarized in chart 5 of Starr's[6] paper, the second remission was not as complete as the first. In another case reported by the same author (chart 7 in his paper), a well marked remission occurred after iodine had been omitted for sixty-four days. In chart 4 of the paper by Starr, Segall and Means,[7] it is shown that after the omission of

iodine for eleven days the second remission was not as great as the first in one case, and was just as great in another. Iodine had been given for only eleven and thirteen days, respectively, before it was omitted, and the rate of metabolism rose only to its pre-iodine level when this medication was stopped. Coller[11] said: "If a recurrence with the continued use of iodine has occurred, there will be an exacerbation of symptoms when iodine is stopped. After a certain length of time has elapsed—the optimum time is not clear—the readministration of iodine will cause another remission."

In some patients refractory to iodine after its prolonged administration, Graham[12] observed a "favorable response" to iodine when its administration was resumed after a period of omission of from three to six weeks.

In case 1, the initial short period of iodinization was apparently not associated with the development of refractoriness, whereas the prolonged administration was. When the administration of iodine is begun after a period of omission, the second response is said by some authors to be less marked than the first.[13] The difference between this observation, on the one hand, and that of Coller[11] and ourselves on the other, probably can be accounted for by two factors: (1) Sufficient time may not have been allowed to elapse between the two administrations of iodine.[14] (2) A spontaneous variation may occur in the disease itself.[15]

CLINICAL STATUS OF THE PATIENT DURING THE REFRACTORY PERIOD

In cases 1, 2, 3 and 5, as the rate of metabolism was rising during the administration of iodine, all of the peculiar nervous manifestations of the disease not only were present, but were becoming

11. Coller, F. A.: The Use of Iodine in the Treatment of Goiter, Ann. Clin. Med. **5**:91, 1926.

12. Graham, A.: Preoperative Iodine Therapy in Toxic Goiter: Indications and Limitations, Am. J. Surg. **2**:354, 1927.

13. Hutton, J. H.: Dangers of Iodine in the Treatment of Goiter, Illinois M. J. **50**:408, 1926. Holmes, M. E.: The Value and Danger of Iodine in Thyroid Disease, New York State J. Med. **27**:538, 1927.

14. This is perhaps illustrated in chart 7 of the paper by Plummer and Boothby (The Value of Iodine in Exophthalmic Goiter, J. Iowa State M. Soc. **14**:66, 1924). There was much less reduction in basal metabolism during the second administration of iodine than during the first. Iodine had been omitted for only eight days, however. During the third administration, after iodine had been omitted for seventy-four days, the response was just as striking as initially. The data are somewhat complicated by ligations but nevertheless illustrate the point.

15. Thompson, Brailey, Thompson and Thorp (footnote 2, second reference).

more intense. When the rate of metabolism finally reached its highest point during the administration of iodine, all of the patients were worse than they had been previously. Their clinical condition was indistinguishable in type from their pre-iodine condition, except that all the signs and symptoms of exophthalmic goiter were more intense. In the second and third cases they became somewhat more intense on the omission of iodine, but in the first case, not only did no further increase occur, but, as stated before, there even occurred a slight spontaneous decrease in the severity of the disease when iodine was omitted. In case 4 after the patient had had 30 drops of the compound solution of iodine daily for one month before entering the hospital, the nervous phenomena of the disease were indistinguishable in type from those in a patient with a severe case of exophthalmic goiter who has never had iodine, and they did not increase in intensity following the omission of iodine. In case 1, the patient's eyes began to be prominent about two months before the omission of compound solution of iodine, and in case 2, about two and one-half weeks before its omission. In both, however, a lid lag was first noticed after the omission of iodine. In case 3, the exophthalmos definitely increased while the rate of metabolism was rising during the administration of iodine, and it appeared to do so in case 5. We have seen an increase in exophthalmos in at least three other patients as the basal metabolic rate was rising during the continuous administration of from about 125 to 250 mg. of iodine daily.

SIZE OF THE DOSE OF IODINE

Several good observers are of the opinion that when the administration of iodine is long continued, aggravation of symptoms is more apt to be associated with the administration of large doses than with that of small doses.[16] However, we know of no carefully controlled work that has been done to show whether or not a group of patients with exophthalmic goiter is more apt to grow worse during the prolonged administration of large doses of iodine than a similar group during the prolonged administration of small doses. On several occasions we have seen the disease grow worse following a temporary improvement during the continuous administration of small doses (1 drop of the compound solution of iodine daily), just as during the

16. Neisser, E.: Ueber Jodbehandlung bei Thyreotoxikose, Berl. klin. Wchnschr. **57**:461, 1920. Fraser, F. R.: Iodine in Exophthalmic Goitre, Brit. M. J. **1**:1, 1925. Cowell, S. J., and Mellanby, E.: Effect of Iodine on Hyperthyroidism in Man, Quart. J. Med. **18**:1, 1924. Marine, D.: Iodine in the Treatment of Diseases of the Thyroid Gland, Medicine **6**:127, 1927.

continuous administration of large doses (30 drops daily [17]). Charts 1 and 3 are perhaps examples of this, although the temporary administration of large doses complicates the picture somewhat. We [18] have shown that what are commonly regarded as small doses (from 3 to 5 drops of compound solution of iodine daily) are in reality considerably greater than the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases. So far as the cases in this series are concerned, it may be noted that in the first case the temporary administration of large doses (from 30 to 90 drops daily) appeared to accelerate slightly the rate at which the condition became refractory to 1 drop daily. In the second case, it is not known what would have happened to the metabolism had the administration of 5 drops daily been continued and 30 drops not been given, or had 1 drop daily been continued and the larger doses of 5 and 30 drops daily not been given.

A fairly large number of observations published elsewhere [19] suggested that the most important factor in determining the course of the basal metabolism during the prolonged administration of iodine may be the severity of the disease and not the size of the dose of iodine. Thus in mild cases the basal metabolism can often be held at or near the normal level for months to years by the prolonged administration of iodine. On the other hand, severe and moderately severe cases rarely show more than temporary improvement.[17] Therefore, refractoriness seems to occur primarily in the moderately severe and severe cases of the disease. The fact that the rate of metabolism began to rise sooner and rose more rapidly in case 5 than in cases 1, 2 and 3 may be attributed to the greater severity of the disease as well as to the larger doses of iodine. Moreover, it is possible that while the acute rheumatic fever that was present on admission to the hospital did not prevent a marked temporary improvement during the administration of iodine, it may have tended to shorten the duration of this improvement.

While the data in this paper demonstrate primarily that complete refractoriness to small doses of iodine may develop, it appears to us probable that complete refractoriness to large doses may also develop. For example, in case 4 the condition was apparently refractory to large doses on the patient's admission to the hospital, that is, after one month's administration. In case 5 the condition became at least partially refractory to large doses, as judged by the marked increase in

17. Thompson, Thompson, Brailey and Cohen (footnote 3, second reference).

18. Footnote 2. Thompson, Thorp, Thompson and Cohen (footnote 8).

19. Thompson, Thompson, Brailey and Cohen (footnote 3). Thompson, W. O., Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, Arch. Int. Med. **46**:946 (Dec.) 1930.

the basal metabolic rate and in the severity of signs and symptoms before operation and the thyroid crisis after operation. Moreover, for some reason that at present is not clear, a small percentage of patients show no response initially to the administration of large doses of iodine.

COMMENT

There are at least two possible explanations of the phenomena observed:

1. Iodine in no way alters the course of the disease, and, during its prolonged administration, the rate of basal metabolism at any point is just what it would have been if the administration of iodine had been started shortly before. In other words, if the condition becomes completely refractory to iodine at a certain time during administration, it would have been completely refractory at exactly the same time if no iodine had been administered, and iodine plays no rôle in the development of the period of refractoriness.

2. It is possible that in some cases during the administration of iodine some reaction to it occurs which tends to counteract its beneficial effects. The period of refractoriness may thus be thought of as an end-result of the reaction to iodine.

At present neither hypothesis can be proved or disproved. There are certain facts that appear to support one hypothesis and certain facts that appear to support the other. In favor of the first are the following observations:

1. A few patients appear to be initially refractory to iodine.

2. In some patients the effect of iodine on the basal metabolism and clinical picture may vary markedly from time to time.[20]

3. In one mild case of the disease we[21] observed that the basal metabolism both rose and fell during the continuous administration of iodine under the same conditions of activity.

It was perhaps for similar reasons that Means,[22] on the basis of Plummer's hypothesis,[1] was led to say:

> The "thyrotoxicosis of exophthalmic goiter" may be thought of "as made up of two components, one of which can be held in abeyance so long as an excess of iodine is present; this we may call A, the other of which, influenced by iodine, we may

20. Thompson, Brailey, Thompson and Thorp (footnote 2, second reference). Thompson, Thompson, Brailey and Cohen (footnote 3, second reference).

21. Thompson, Thompson, Brailey and Cohen (footnote 3, second reference): Myxedema During the Administration of Iodin in Exophthalmic Goiter, Am. J. M. Sc. **179**:733 (June) 1930.

22. Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 150.

call B. . . . The ratio of the components A : B will vary from patient to patient, from place to place, and in the same patient from time to time. As the disease runs its course important changes in the ratio undoubtedly occur, and the relative magnitude of the influence to be had by saturating the patient with iodine will vary accordingly."

In favor of the second hypothesis are the following observations:

1. Whereas the reduction in the rate of basal metabolism during the administration of iodine varies considerably from patient to patient, it is usually well marked, and cases that show no reduction are not common, provided iodine has not been administered shortly before. If refractoriness to iodine may be regarded as a stage in the course of most cases of exophthalmic goiter, it seems strange that a larger number of patients are not initially refractory to iodine.

2. As previously mentioned, doses of iodine inadequate to cause any reduction in the rate of basal metabolism may sometimes interfere with the effect of much larger doses administered immediately afterward.

3. When iodine was omitted as the rate of basal metabolism was rising in cases 2 and 3, the response appeared to be recovery from the refractoriness and not a further development to complete refractoriness. At least in the first patient, the refractoriness had disappeared after an interval of twenty-four days. In the second patient, it had disappeared after an interval of fifty days (how much sooner is unknown).

The criticism can always be made that we do not know what the course of the basal metabolism would have been in our cases had iodine never been omitted. For this reason, the natural course of the disease can usually be invoked to explain everything that happens to patients with exophthalmic goiter.

Regardless of what the explanation of these findings may be, our data indicate that the peculiar nervous manifestations of exophthalmic goiter may be present during the administration of iodine in both small and large doses. Thus, in patients with this disease, while iodine is being administered, exophthalmos may first appear or increase, and the remainder of a clinical syndrome that we are unable to distinguish from that of exophthalmic goiter may grow more intense. Lahey[23] reported several cases in patients who came to his clinic in the crisis of the disease and who died before operative procedures could be contemplated, in spite of "the most heroic measures," including the administration of iodine in large doses. This has some bearing on the treatment for the disease. For example, it is sometimes claimed that the height of the basal metabolic rate is not a criterion of the operative

23. Lahey, F. H.: The Management of Goiter, J. Indiana M. A. **23**:117, 1930

risk of the patient and that, so long as iodine is being administered in excess, the patient is a good risk, regardless of what happens to the rate of basal metabolism. The reason given for this is that operative mortality is bound up primarily with the "bad product" (i. e., component A) and not with the "good product" (component B); and, on theoretical grounds, the "bad product" is said to be always completely under control during the administration of iodine in excess. While it is true that the height of the rate of basal metabolism is not the only criterion for determining the risk, the last part of this claim seems questionable. For example, when the patient in case 5 was first brought to the operating room, he behaved as patients with severe cases of the disease did in similar circumstances before the days of the use of iodine, and operation had to be postponed. When operation finally was performed, however, he had a typical postoperative crisis, with marked nervousness, vomiting, fever, tachycardia and delirium, resulting in death. This postoperative reaction was indistinguishable from that presented by patients with severe cases of the disease before iodine was used for treatment.

We have occasionally seen similar postoperative reactions which were not fatal in patients who had received iodine in large doses for only the usual time before operation (from ten to fourteen days), notably in those who had not responded very well to it, but also in patients who had shown a satisfactory response. The reactions to which we refer are characterized by marked nervousness, thrashing about in bed, a wild expression in the eyes, fever, marked tachycardia and occasionally delirium, vomiting and auricular fibrillation, and we are unable to distinguish them from those that occurred before the days of treatment with iodine. Lahey [24] and Clute [25] reported severe postoperative reactions, some of which were fatal, in patients who had been given iodine in large doses both before and after operation. De Courcy,[26] Dunhill,[27] Graham [12] and Kessel and Hyman [28] expressed the belief that some patients remain poor operative risks in spite of

24. Lahey, F. H.: The Use of Iodine in Goitre, Boston M. & S. J. **193**:487, 1925; The Management of Post-Thyroidectomy Complications, S. Clin. North America **8**:13, 1928.

25. Clute, H. M.: Effect of Compound Solution of Iodin and Rest in Surgery of Exophthalmic Goiter, J. A. M. A. **86**:105 (Jan. 9) 1926.

26. De Courcy, J. L.: Review of 3,600 Thyroidectomies, Am. J. Surg. **2**:225, 1927.

27. Dunhill, T. P.: Toxic Goitre, Brit. J. Surg. **17**:424, 1930.

28. Kessel, L., and Hyman, H. T.: Exophthalmic Goiter and the Involuntary Nervous System: XVI. The Influence of Subtotal Thyroidectomy With and Without Compound Solution of Iodine on the Course of the Disease, Arch. Int. Med. **40**:623 (Nov.) 1927.

preparation with iodine. While one of the chief benefits of iodine has been a marked decrease in the number of postoperative crises, the fact that iodine has been administered in large doses for ten days or more before operation is in itself not an absolute guarantee that there will not be one.

It may thus be said that regardless of the theoretical interpretation of these phenomena, they suggest the following therapeutic applications: 1. In severe cases of the disease, operation should be performed as soon as the metabolism reaches a level during the administration of iodine, because the beneficial effects in such cases may be of short duration. 2. If in such cases, however, operation is slightly delayed and the rate of metabolism starts to rise rapidly soon after the initial drop, operation should not be performed until iodine has been omitted for a short time, because in the presence of a rapidly rising rate of metabolism operation appears to be unsafe. A short period of omission of iodine may cause the refractoriness to disappear and make the patient a better operative risk.

Most observers have seemed loathe to omit iodine if the rate of metabolism is rising. This attitude is based on the rather widespread belief that the effect of iodine never completely wears off while it is being administered, regardless of what happens to the basal metabolism. Our observations suggest that in such a stage of the disease the patient may be largely refractory to iodine; that its continued administration may be associated with a still further increase in the severity of the disease; that the rate of metabolism may not rise much higher following its omission, and that its omission may be followed by the disappearance of the refractoriness. During the period in which iodine is omitted, the patient should be at rest in bed. Medication probably does not need to be discontinued longer than from three to four weeks. Iodine may then be readministered, and if the basal metabolism drops, operation may be performed with comparative safety.

Campbell,[29] Graham,[12] De Courcy[26] and Goetsch[30] expressed the belief that operation on a patient who shows a high rate of metabolism and who is very ill after the prolonged administration of iodine may cause death. Campbell is of the opinion that after a short period of freedom from iodine, such patients again respond to it and become good operative risks. It is said to be the custom at the Toronto General Hospital to omit iodine for a short time in all such cases.[31]

29. Campbell, W. R.: Personal communication to the authors.
30. Goetsch (footnote 9).
31. Graham, D.: Personal communication to the authors.

In our series there is a contrast between the patient in case 5, who was operated on while the metabolic rate was rising rapidly during the administration of iodine and who died from a typical postoperative crisis, and the first four patients, in whose cases iodine was omitted when the metabolic rate was rising or was very high and who were not operated on until the refractoriness to iodine had disappeared, when convalescence was uneventful. It would perhaps have been preferable to have regarded the goiter in case 5 as the major problem and to have proceeded with the operation without waiting to determine whether the rheumatic fever would recur when salicylates were omitted. Since this was not done, it would seem that operation should have been postponed until iodine had been omitted for a short time.

In cases of the disease that are only moderately severe, it is our impression that the rate of metabolism usually remains depressed for several weeks before starting to rise, and that the rise is usually slow. In this type of case we doubt that any harm is done by delaying operation for a short time while iodine is being administered. Furthermore, we doubt that a very slowly rising rate of metabolism during the administration of iodine is a contraindication to operation, unless the metabolism has already attained a high level. It is also true that the severity of the postoperative reaction cannot be predicted entirely by the preoperative height of the rate of metabolism. Some patients who show little or no reduction in the rate during the administration of iodine have only moderate postoperative reactions (case 6). Like all other biologic phenomena, the response of patients with exophthalmic goiter to iodine is variable.

SUMMARY AND CONCLUSIONS

During the prolonged continuous administration of iodine one patient with exophthalmic goiter, after showing a remission, became completely refractory to 6 mg. of iodine daily, a dose that was at other times sufficient to produce a maximum reduction in the basal metabolism. Four other patients became at least partially refractory to iodine during its prolonged administration in doses of from 6 mg. to 250 mg. daily.

In four of the preceding five cases, iodine was omitted and the refractoriness disappeared.

The fifth patient was operated on when the metabolism was rising rapidly during the continuous administration of iodine, and he died about forty hours afterward from a typical postoperative crisis. This reaction was indistinguishable from those previously seen in patients who were operated on without receiving iodine.

The exact length of time necessary for the refractoriness to disappear completely when iodine is omitted is unknown; it was observed to do so within twenty-four days.

When the metabolism reached its highest point during the administration of iodine, the disease was more severe than it had previously been, and all the peculiar nervous manifestations not only were present, but were more intense. In two patients, exophthalmos was first noted as the rate of metabolism was rising during the continuous administration of small doses of iodine, and in the other two, it became more marked under these circumstances.

The reactions appear to be more characteristic of severe cases than of mild cases.

Our observations do not appear to support the hypothesis that the peculiar nervous manifestations of exophthalmic goiter are always under control as long as an excess of iodine is being administered.

In severe cases operation should be performed as soon as a maximum reduction in the rate of basal metabolism occurs.

In any case, when the metabolism has increased markedly during the administration of iodine, it is probably wise to postpone operation until after this medication has been omitted for from three to four weeks, with the patient at rest in bed, to allow the refractoriness to disappear, and until the administration of iodine has been resumed.

Certain phenomena that may be related to the development of refractoriness to treatment with iodine are described.

CONGESTIVE HEART FAILURE

X. THE MEASUREMENT OF VENTILATION AS A TEST OF CARDIAC FUNCTION *

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In the examination of the heart, various methods are employed. Most of them are of value, but none of them afford an accurate index as to the functional capacity of the heart. The most commonly employed method of estimating the functional capacity consists in counting the pulse before and after standardized exercise. Concerning such tests, Sir James Mackenzie [1] stated:

> One of the most profitless lines of investigation has been those numerous and elaborate attempts to discover the condition of the heart's efficiency by various tests in which bodily effort is employed and the heart rate taken as a standard.

With regard to the measurement of cardiac capacity for work, Sir Thomas Lewis [2] said:

> Innumerable tests have been, and continue to be devised to answer this question; they are based mainly upon pulse and blood pressure readings . . . . Experience of such tests have convinced me that they have little practical value, and tending as they often do to become rules of thumb, they likewise become most undesirable.

Our own experience with the pulse rate test has not been extensive. In the majority of instances patients with cardiac disease exhibit a greater and more prolonged increase than normal persons after performing the same exercise, but the exceptions to this rule are so frequent as to make the method of little value. Examples of these exceptions are shown in table 1. The exercise was carefully standardized. With mild exercise, the response of the normal subject and of the patient with advanced cardiac disease were practically identical. After more severe effort, the patient with early organic cardiac disease returned to normal quicker than did either the normal subject or the one with cardiac neurosis.

* Submitted for publication, Nov. 8, 1930.

* From the Department of Medicine of Vanderbilt University, Nashville, Tenn.

1. Mackenzie, James: Diseases of the Heart, ed. 4, London, Oxford University Press, 1925, p. 114.

2. Lewis, Thomas: Early Signs of Cardiac Failure of the Congestive Type, Brit. M. J. **1**:849, 1930.

Most clinicians would agree that at the present time there is only one reliable index to cardiac function and that this is the degree of dyspnea during and after effort. But dyspnea is a subjective phenomenon and hence as such cannot be expressed accurately in quantitative terms. The present research is concerned with an effort to arrive at a quantitative concept of dyspnea by means of respiratory measurements. Most of our present knowledge along these lines has come from the important studies of Francis W. Peabody and his co-workers,[3] and the present study is in large measure based on the fundamental concepts developed by them.

METHOD

In general, the method first employed consisted of measuring the amount of air expired by the subject during a period of standardized exercise and for a certain period after the exercise was ended. The apparatus used is shown in

TABLE 1.—*The Pulse Rate After Exercise*

Subject	Clinical Data	Pulse Rate: Before Exercise	After Exercise: 1 Min.	2 Min.	3 Min.	4 Min.	5 Min.	6 Min.	7 Min.	Comment
W. G. H.	Normal.....	88	100	92	90	86	90	90	88	
E. G.	Syphilis; aortic insufficiency; has had three breaks in compensation...	82	96	88	86	84	82	80	80	Mild exercise
W. G. H.	Normal.....	88	144	124	124	112	106	104	102	
R. L. M.	Cardiac neurosis..	106	152	134	126	126	122	114	116	
V. B. M.	Hypertension; slight cardiac hypertrophy; no congestive cardiac failure.....	104	144	120	112	106	108	104	106	Severe exercise

figure 1. A platform 64 cm. broad was supported at each side by two steps, each 16 cm. high. The subject wore a mask with inlet and outlet valves. The outlet valve was connected by means of flexible rubber tubing with a two-way trap, which in turn was connected with two Tissot spirometers. The expired air was collected in one spirometer during the exercise and in the other after the exercise. (It happened that a very large spirometer was not available and hence we used two smaller ones. A gas meter would serve the purpose equally well and has the advantage of being cheaper.)

In each instance the duration of the exercise was two minutes. At the end of this period the subject rested quietly in a comfortable chair for five minutes, during which time the ventilation was measured. This time is designated as the "after period." Four different rates of exercise were used. The mildest type consisted of six "round-trips" (i.e., over the steps and back) in two minutes. The others consisted of twelve, sixteen and twenty-four "round-trips," respectively, in two minutes. The operator counted with a stopwatch in order to

3. Peabody, Francis W., et al.: Clinical Studies of Respiration, Arch. Int. Med **10**:846 (Nov.); 955 (Dec.) 1915; **20**:433 and 443 (Sept.); 468 (Oct.) 1917; **28**:501 (Nov.) 1921; **29**:236 (Feb.); 277 (March) 1921.

assure that the rate of performance remained relatively constant. For purposes of brevity, the graded exercises will be referred to in the remainder of this paper as, in order of increasing severity, exercise I, II, III and IV, respectively. Exercise I is extremely slow and can be performed by any patient who is able to get out of bed. Exercise II is approximately equivalent to walking at an ordinary pace, and exercise III to rapid walking. Exercise IV is about as severe as a rather slow run. Normal subjects experienced little or no dyspnea with the first three grades, but were slightly to moderately dyspneic toward the end of exercise IV. Exercise IV is rather too severe for any subjects except normal persons

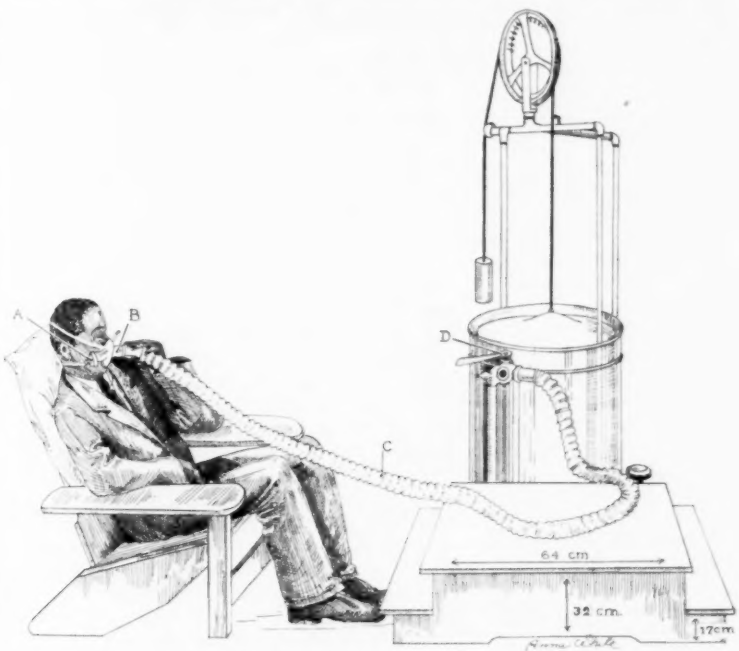

Fig. 1.—The subject inhales through the inlet valve *A*, and exhales through the expiratory valve *B*. By means of the flexible corrugated rubber tubing *C*, the expired air passes through the three-way tap *D*. During the preliminary rest period, the expired air passes back into the room. At the beginning of the first exercise, the tap is turned, and for the two minutes of the exercise and the succeeding five minutes of the after period the expired air is collected in the spirometer, and the total volume for the seven minute period is measured. The tap *D* is then turned to room air and the spirometer emptied. In like manner the measurements for exercise II and III are made. Although we used a spirometer, a gas meter will serve the purpose equally well and is cheaper.

and patients with very early cardiac disease. After reviewing all of our data we do not believe that the additional information gained from exercise IV is of sufficient value to warrant the additional time and the respiratory discomfort involved.

Consequently, we have decided to employ only exercises I, II and III in our future work.

The usual plan consisted of beginning with exercise I, and then, after the usual five minute after period, having the subject perform exercise II, followed by the after period, and so on. However, when one degree of exercise produced moderate or severe respiratory distress, the succeeding grades of work were not done.

An attempt was made to evaluate the degree of dyspnea in each instance. Such evaluation is extremely rough and subject to great inaccuracies, but as a rule the observation of the patient's facial expression, alertness and type of respiratory movements, when coupled with his own statement allowed one to judge whether distress was absent, slight, moderate or severe. In the majority of subjects the objective signs of distress as recorded by the operator of the experiment agreed fairly well with the person's statement concerning the dyspnea. However, patients with cardiac neurosis usually complained of more dyspnea than their objective states indicated.

In the first experiments an attempt was made to separate the excess ventilation due to the exercise from the total ventilation. This was done by measuring the ventilation during resting before the exercise and subtracting this value from the ventilation during and after the exercise. However, it was seen that although ventilation during and after a given exercise was fairly constant in the same person from day to day, the ventilation during resting varied rather markedly, and a large error was introduced. (This disadvantage can be overcome by the use of fore periods of one-half hour or more, but in such cases the subject becomes tired of the mask and is likely to be restless.) For this reason the fore period was abandoned, and calculations were made on the basis of the ventilation during the two minute period of exercise plus that during the five minute after period. Such a method of calculating the results has the disadvantage of expressing the values in terms of ventilation for the entire seven minute period rather than per minute, as is customary. However, the after period is necessary, as a large fraction of the excess ventilation comes after, not during, the exercise, particularly in dyspneic subjects. To divide the total amount of ventilation by 7 and call this value ventilation per minute would be absurd, because the actual ventilation varies from minute to minute, being greatest during the second minute of the exercise and the first minute thereafter. Therefore, it is important to remember that the figures reported are arbitrary in the sense that they are obtained for a selected exercise, performed at a chosen rate for a given time.

In order to compare one subject with another, the height and weight of each subject were taken, the surface area was calculated from the Du Bois chart, and the values were expressed in terms of liters per square meter.

The vital capacity was also determined in each subject and expressed in terms of liters per square meter. The reasons for this will be given.

In calculating the values the customary method of reducing ventilation volume to liters at standard conditions has been followed. The values for vital capacity have not been so corrected but have been calculated, as is usual in respiratory experiments, for the prevailing temperature and barometric pressure.

RESULTS

The Relation of Dyspnea to Respiratory Measurements.—The Variation of the Ventilation: Duplicate observations on six normal subjects are shown in table 2, the values being expressed in terms of liters per square meter. It can be seen that the maximum variation in the same

subject performing the same exercise on different days is 15 per cent, but that the usual variation is considerably less than 10 per cent. Different subjects vary by 20 per cent or more in their ventilations per square meter for the same exercise. The greatest variations occurred in exercise IV, which is sufficiently severe to make the question of the degree of muscular training important. For this reason, as well as for others, this part of the test can well be omitted.

The Correlation between Dyspnea and the Ventilation per Square Meter: The data in table 3 are based on 304 tests and point to a defi-

TABLE 2.—*Duplicate Measurements of the Ventilation During and After Test Exercises*

		Ventilation per Square Meter, Liters				Percentage Difference, Liters				
Subject	Date	For Exercise I	For Exercise II	For Exercise III	For Exercise IV	For Exercise I	For Exercise II	For Exercise III	For Exercise IV	Sex
M. H.	6/18/30	36.0	44.9	48.5	85.4	1.6	2.7	1.2	13.6	Female
	6/24/30	35.4	43.7	49.1	75.5					
M. M. T.	6/17/30	37.6	43.7	55.9	76.4	14.0	5.1	8.8	6.3	Female
	6/20/30	42.9	46.0	51.3	81.3					
E. C.	6/17/30	34.4	40.9	52.8	83.8	5.7	1.5	3.8	5.6	Female
	6/24/30	36.4	41.5	50.8	79.2					
J. A. C.	6/15/30	36.6	45.7	55.9	74.2	1.6	2.3	6.3	13.2	Male
	7/16/30	36.0	44.6	50.5	65.5					
F. C. T.	6/19/30	39.9	45.7	55.8	74.7	8.6	7.7	15.0	10.6	Male
	7/24/30	36.7	42.4	48.5	67.5					
T. R. H.	6/15/30	41.2	46.7	59.1	83.5	2.5	5.0	5.2	4.5	Male
	6/21/30	42.2	44.4	56.1	79.9					

TABLE 3.—*The Relation Between Dyspnea and the Ventilation Per Square Meter*

		Ventilation per Square Meter, Liters								
Number of Tests	Degree of Dyspnea	Less Than 30	30 to 40	40 to 50	50 to 60	60 to 70	70 to 80	80 to 90	90 to 100	More Than 100
179	None	0	41	97	39	2	0	0	0	0
84	Slight (+)	0	4	7	25	23	14	11	0	0
41	Moderate (++)	0	0	2	5	9	10	8	6	1
16	Severe (+++)	0	0	0	1	4	3	5	1	2

nite relationship between the amount of ventilation and the degree of distress. For instance, it can be seen that when the ventilation per square meter was above 60 liters, dyspnea of some degree almost invariably occurred. However, there is little evidence from the table to indicate whether the probabilities are that any level of ventilation between 60 and 90 liters would be associated with slight, moderate or severe dyspnea. It is evident that the ventilation per square meter is a poor index to the severity of dyspnea.

The Relation of Vital Capacity to Dyspnea: As has been stated, our interest was in dyspnea as such rather than in ventilation. It was soon learned that subjective respiratory distress was not directly proportional to ventilation per square meter. Thus, patients with abnormal

TABLE 4.—*The Relation of Diminished Vital Capacity to Dyspnea*

Subject	Date	Diagnosis	Vital Capacity per Square Meter, Liters	Exercise I			Exercise II			Exercise III			Exercise IV		
				Ventilation per Square Meter, Liters	Dyspnea	Ventilation / Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation / Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation / Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation / Vital Capacity
F. C. T.	6/19/30	Normal	2.36	39.9	0	16.9	45.7	0	19.4	55.8	0	23.6	74.7	+	31.7
	8/ 4/30	With tight binder around chest and abdomen	1.93	36.6	0	19.0	48.9	0	25.3	49.3	+	25.6	78.6	++	40.7
T. R. H.	6/21/30	Normal	2.55	42.2	0	16.5	44.4	0	17.4	56.1	0	22.0	79.9	+	31.4
	8/ 4/30	With tight binder around chest and abdomen	1.99	40.6	0	20.4	48.5	0	24.3	52.8	+	26.7	76.8	++	38.6
A. B.	8/20/30	Pneumothorax	1.62	40.8	0	25.2	46.2	+	28.6	54.4	+	33.5			
E. J.	7/14/30	Scoliosis	1.78	46.4	0	25.4	49.1	+	31.0	58.1	+	36.8	79.1	++	50.1

lungs may have a normal ventilation per square meter and yet be distinctly more dyspneic than a normal person. In table 4 are shown values on two normal subjects with and without tight canvas binders wrapped around their chests and abdomens. Although the vital capacities were reduced only about 10 per cent, the subjects experienced definitely more than their usual discomfort with the severe exercises. Both of these subjects performed the test on numerous occasions under various conditions, and the statements as to the dyspnea are probably reliable. However, the relation of vital capacity to dyspnea is brought out more clearly in the last two subjects in table 4. These persons had abnormally low vital capacities owing to disease. For the various exercises their values for ventilation per square meter were almost exactly the same as those of the two normal subjects, but their distress was definitely greater.

TABLE 5.—*The Relation Between Dyspnea and the Ratio:* $\frac{\text{ventilation}}{\text{vital capacity}}$

Number of Tests	Degree of Dyspnea	Ventilation : Vital Capacity							Comment
		Less Than 15	15 to 25	25 to 35	35 to 45	45 to 55	55 to 65	More Than 65	
163	None	5	127	47	0	0	0	0	Only 9 tests above 30; 94 per cent of tests below 30
84	Slight (+)	0	5	52	22	5	0	0	No test below 20; 80 per cent of tests between 25 and 40
41	Moderate (++)	0	0	5	21	12	3	0	No tests below 30; 80 per cent of tests between 35 and 55
16	Severe (+++)	0	0	0	1	5	5	5	Three tests below 50; 80 per cent of tests above 50

These observations are confirmatory of the studies of Peabody,[3] who pointed out the great importance of decreased vital capacity in the production of dyspnea.

The Correlation between the Ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ and the Degree of Dyspnea: The data in table 4 are in agreement with general clinical experience that, roughly speaking, dyspnea is directly proportional to ventilation and inversely proportional to vital capacity. The ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ should therefore be a better index of respiratory distress than ventilation alone. That this is actually the case is shown by a study of table 5, and a comparison of it with table 3. The total ventilation (for the seven minute period) divided by the vital capacity was compared with the degree of distress in 304 tests on more than 40 subjects (including normal persons and subjects with pathologic conditions who performed exercises of varying severity). Observations on subjects with cardiac neurosis and on persons with respiratory obstruction were omitted from this tabulation for reasons that will be men-

TABLE 6.—*The Effect of Respiratory Resistance on the Ventilation*

Subject	Date	Experimental Condition	Exercise I			Exercise II			Exercise III			Exercise IV		
			Ventilation per Square Meter, Liters	Dyspnea	Ventilation Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Vital Capacity	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Vital Capacity
F. C. T.	6/19/30	Normal; vital capacity 2.36 liters per square meter.....	39.9	0	16.9	45.7	0	19.4	55.8	0	23.6	74.7	+	31.7
	8/ 5/30	Inspirating and expirating valves occluded by corks with holes 4 mm. in diameter; vital capacity 2.23 liters per square meter.....	32.8	0	14.7	38.9	+	17.4	46.7	+	20.9	67.0	+++	30.0
T. R. H.	6/15/30	Normal; vital capacity 2.55 liters per square meter.....	41.2	0	16.2	46.7	0	18.3	59.1	0	23.2	83.5	+	32.7
	8/ 5/30	Inspiratory and expiratory valves occluded by corks with holes 4 mm. in diameter; vital capacity 2.56 liters per square meter.....	36.7	0	14.3	42.5	+	16.6	51.4	++	20.1	71.9	+++	28.1

tioned later. The clinical note as to the maximum degree of dyspnea experienced during the test was recorded before the respiratory measurements were completed. "No dyspnea" was recorded in 163 instances. In none of these was the ratio $\frac{\text{ventilation}}{\text{vital capacity}}$ above 35, and in only 9 observations was this quotient greater than 30. When "dyspnea +" was recorded, the ratio was between 25 and 40 in 65 of the 84 instances, being below 25 in only 5 cases. Moderate (++) dyspnea was usually associated with a quotient of from 35 to 55, and values above the latter level were rare except in patients who seemed to be in severe distress. When one considers the great difficulty and the obvious high percentage of error in classifying the degree of dyspnea, it seems that this ratio is a fairly accurate expression of respiratory distress.

The Importance of the Nutritional State: One naturally expects obese persons to show greater ventilation than other subjects for a given exercise. As a corollary, one wonders whether thin people have less ventilation. In order to study these matters, observations were made on 16 healthy subjects. Their "ideal weights" were calculated according to the formulas:

Ideal weight for males=110 pounds for 5 feet and 5½ pounds for each additional inch.

Ideal weight for females=100 pounds for 5 feet and 5 pounds for each additional inch.

Five subjects were more than 10 per cent overweight; 6 were within 10 per cent of their theoretical ideal weight; 5 were more than 10 per cent underweight. The vital capacity per unit of body surface was least in the obese group and greatest in the normal group.

The values for $\frac{\text{ventilation}}{\text{vital capacity}}$ were considerably higher for the obese subjects and tended to be a little lower in the undernourished subjects than in the group with a more normal nutritional status. The data are shown in table 7.

Such a comparison obviously puts the obese subject at a disadvantage, because his vital capacity is likely to be somewhat subnormal, and since he does more work with the exercise one would expect his ventilation to be somewhat higher. It is true that on the whole he is more dyspneic and therefore the value $\frac{\text{ventilation}}{\text{vital capacity}}$ which, as we have shown, is proportional to dyspnea, should be higher. However, for purposes of comparison with persons suffering from disease, it is desirable to have standards that will reflect the degree of dyspnea due to disease, rather than the dyspnea due to the nutritional state. Therefore, an attempt was made to recalculate the values in such a way as to eliminate the rather marked variation dependent on the body weight. The results of the first attempt at correcting for body weight are shown

in the right hand portion of table 7. These values were obtained by the product of $\frac{\text{ventilation}}{\text{vital capacity}} \times \frac{\text{ideal weight}}{\text{actual weight}}$. By such a method of calculation, the obese subjects have the lowest values and the thin subjects the highest. If this method of calculation is adopted, the fat people are more efficient than the subjects with normal nutritional status. This is illogical. One must remember that the test includes a two minute period of exercise plus a five minute after period. The total ventilation is composed of two factors: (1) a ventilation during resting that is proportional to metabolism and hence to body surface, and (2) an excess ventilation due to work done, and hence proportional not to body surface but to body weight. Therefore, it seems logical to assume that

TABLE 7.—*The Relation of the Nutritional State to the Ventilation*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Ventilation / Vital Capacity				Ventilation / Vital Capacity × Ideal Weight / Actual Weight				Comment
				Exercise I	Exercise II	Exercise III	Exercise IV	Exercise I	Exercise II	Exercise III	Exercise IV	
J. W. H.	71.0	218	2.09	18.6	20.9	26.3	39.0	14.5	17.4	20.5	30.4	More than 10 per cent over weight
E. C.	62.0	144	1.92	20.0	21.3	25.6	46.0	16.3	17.5	21.0	37.8	
W. G. H.	67.5	187	1.93	19.3	25.5	28.4	42.3	15.6	20.6	22.9	34.2	
E. P. C.	71.5	205	1.90	23.1	26.5	32.7	40.5	19.6	22.4	27.6	34.2	
G. E. C.	68.0	198	1.99	19.5	22.1	26.6	....	15.2	17.3	20.8	....	
Average			1.97	20.1	23.3	27.9	42.1	16.2	19.0	22.6	30.2	
J. A. C.	67.5	145	2.37	15.1	18.8	22.7	29.0	15.7	19.6	23.6	30.2	Within 10 per cent of ideal weight
T. R. H.	66.5	146	2.55	16.4	17.9	21.9	31.2	16.4	17.9	21.9	31.2	
F. C. T.	69.5	150	2.36	16.4	18.8	22.2	30.4	17.6	20.1	23.8	32.6	
J. G. M.	70.0	172	2.19	18.7	20.4	24.4	38.4	17.9	19.6	23.4	36.9	
W. J. E.	67.5	139	2.42	16.4	19.0	22.6	31.4	17.8	20.6	24.5	34.1	
H. F.	65.0	123	2.23	18.7	23.0	25.4	37.8	18.9	23.4	25.9	38.5	
Average			2.33	16.9	19.6	23.2	33.0	17.4	20.2	23.9	35.9	
M. M. T.	66.0	108	2.32	15.7	18.7	21.5	29.8	18.8	22.5	25.9	35.9	More than 10 per cent under-weight
B. W. H.	65.0	102	2.08	17.1	21.1	23.4	36.2	21.0	26.0	28.7	44.3	
V. T.	61.0	92	2.18	16.1	18.6	20.1	26.8	18.5	21.4	23.1	30.8	
F. J.	63.0	103	2.02	15.5	22.9	25.3	41.5	17.4	25.5	28.2	46.3	
E. J.	67.5	131	2.18	15.5	18.4	21.2	29.2	17.5	20.8	24.0	33.0	
Average			2.16	16.0	19.8	22.3	32.7	18.6	23.2	26.0	38.0	

during the test the ventilation should be proportional not to body surface or to body weight, but to the mean between the two. According to such a concept, the correct formula for calculation should be:

$$\frac{\text{Distress (independent of nutritional state) due to exercise}}{\text{ventilation per square meter}} = \frac{\text{ventilation per square meter}}{\text{vital capacity per square meter}} + \left[\frac{\text{ventilation per square meter}}{\text{vital capacity per square meter}} \times \frac{\text{ideal weight}}{\text{actual weight}}\right]$$

$$2$$

When this formula is simplified, it becomes:

$$\text{Dyspnea} = \frac{\text{ventilation}}{\text{vital capacity}} \times \left[\frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2}\right]$$

Such an expression should be more or less independent of the nutritional state. That this is actually the case is shown in table 8. The values

here are a mean between those in the right and left portions of table 7. It can be seen that both the individual and the average values lie closer together than in table 7. On the whole, the subjects whose weight is near the theoretical ideal have values slightly lower than the obese groups, the thin subjects being intermediate. This is illustrated in figure 2 in *C*.

Therefore, it seems that unless one is to have a series of different normal standards for subjects of varying degrees of nutrition, the method of calculation described is the best one to use in comparing

TABLE 8.—*The Ventilation Index* in Subjects of Varying Nutritional States*

Subject	Ventilation Index				Comment
	Exercise I	Exercise II	Exercise III	Exercise IV	
J. W. H.	16.6	18.6	23.4	34.7	
E. C.	18.1	19.4	23.3	41.9	
W. G. H.	17.4	23.1	25.5	38.2	More than
C. P. C.†	21.4	24.5	30.1	37.4	10 per cent
G. E. C.	17.3	19.7	23.7	....	overweight
Average	18.1	21.1	25.1	38.2	
J. A. C.	15.4	19.2	23.2	29.6	
T. R. H.	16.4	17.9	21.9	31.2	
F. C. T.	17.0	19.5	23.0	31.5	Within
J. G. M.	18.3	20.0	23.9	37.6	10 per cent of
W. J. E.	17.1	19.8	23.6	32.7	ideal weight
H. F.	18.8	23.2	25.6	38.1	
Average	17.1	20.1	23.5	33.5	
M. M. T.	17.7	20.6	23.7	32.8	
B. H.	19.1	23.6	27.0	40.2	
V. T.	17.3	20.0	21.6	28.8	More than
F. J.	16.5	24.2	26.8	43.9	10 per cent
E. J.	16.5	19.6	22.6	31.1	underweight
Average	17.3	21.5	24.1	35.3	
Grand average	17.4	20.9	24.3	35.7	

* Ventilation index $= \frac{\text{Ventilation}}{\text{Vital capacity}} \times \left[\frac{1 + \frac{\text{Ideal weight}}{\text{Actual weight}}}{2}\right]$

† This subject showed higher values than any other for three of the four points. Although there was no evidence of cardiac disease, both of his parents had it. The upper limits of normal are therefore considered to be 20-25-30-40 for the respective exercises.

normal with pathologic subjects. It should be remembered, however, that the actual dyspnea is proportional to $\frac{\text{ventilation}}{\text{vital capacity}}$.

For the sake of brevity, the values as calculated in table 8 will be referred to as the ventilation index.

The Relation of the Ventilation Index to Sex and Age: As only 16 normal subjects were studied, sufficient data are not yet available to allow a statistical analysis. In table 9 are shown the highest, lowest and normal values for the two sexes. The average values for each exercise are a little higher for females, but the difference is not great. It is likely that studies of a larger number of cases would allow one to prepare separate standards for the two sexes. With the data at hand an attempt to do so seems unwarranted.

The influence of age is depicted in table 10. The data are too meager to draw final conclusions, but one can say that the ventilation index is at least relatively independent of age.

TABLE 9.—*The Influence of Sex on the Ventilation Index of Normal Subjects*

Number of Persons Studied		Ventilation Index				Sex
		Exercise I	Exercise II	Exercise III	Exercise IV	
10	Highest	21.4	24.5	30.1	38.2	Males
	Lowest	15.4	17.9	21.9	29.6	
	Average*	**17.3**	**20.2**	**24.1**	**33.8**	
6	Highest	19.1	24.2	27.0	43.9	Females
	Lowest	16.5	19.0	21.6	28.8	
	Average*	**17.9**	**23.5**	**24.7**	**37.6**	

* Mean of all the values, not of highest and lowest only.

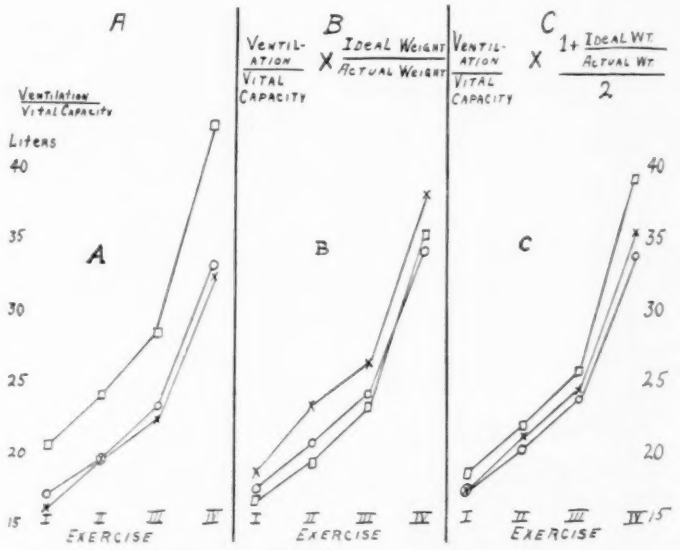

Fig. 2.—*A* shows values for $\frac{\text{ventilation}}{\text{vital capacity}}$ when no correction is made for body weight. These values are seen to be considerably higher in the obese subjects and a little lower in the thin subjects than in the subjects of normal nutritional state. *B* shows the values found when *A* is corrected by multiplying the results by the factor $\frac{\text{ideal weight}}{\text{actual weight}}$. The position for the curve is reversed, the obese group being lowest and the thin group highest. It is evident that this correction factor is too large. In *C*, the mean of the values obtained in *A* and *B* are plotted; the values for all of the subjects fall closer together, the normal group being lowest and the obese group highest. It is evident that the method of correction for body weight used in *C* is preferable to that used in *B*. The line with squares indicate the group of obese subjects; the line with the circles, the normal subjects, and the line with the x's, the thin subjects.

Normal Standards for the Ventilation Index: The normal standards are shown in table 8. The upper limits of normal for the various exercises can be considered as being approximately 20, 25, 30 and 40, respectively. There are a few isolated values above these but no normal subject has a curve with every point above these levels.

The average values for the four exercises are 17.4, 20.9, 24.3 and 35.7, respectively. In normal subjects nine tenths of the values fall within

TABLE 10.—*The Ventilation Index in Relation to Age*

Age Group	Number of Subjects	Average Ventilation Index			
		Exercise I	Exercise II	Exercise III	Exercise IV
Under 30	10	17.3	20.8	24.1	34.8
30 to 50	4	18.3	20.4	24.7	36.6
Over 50	2	17.3	21.2	24.5	35.4

15 per cent of these values, and all of such values fall within 20 per cent of them. Therefore, any values that are more than 20 per cent above these averages are, in all probability, indications of a pathologic condition. For practical purposes, it is simpler to regard any curve with three points above the line 20-25-30-40 as being abnormal. For the sake of clarity a protocol illustrating the final method of calculation is given.

SAMPLE PROTOCOL

Subject: W. H., male, white, aged 59, July 2, 1930.
Height, 67.5 inches. Weight, 187 pounds. Surface area, 1.98 square meters.

Ideal weight, 151 pounds. Weight factor $\left\{1 + \frac{\frac{\text{Ideal weight}}{\text{Actual weight}}}{2}\right\} = 0.90$

Diagnosis: Normal
Temperature of spirometer, 27 C. Barometer, 754 mm. Hg.
(1) Factor for temperature and barometer, 0.875
(2) Factor for spirometer, 1 cm. = 1.59 liters.
(3) Corrected factor for spirometer, (1) × (2) = 1.39.
Vital capacity, 3.82 liters.
Vital capacity per square meter, 1.93 liters.

	Exercise I	Exercise II	Exercise III	Exercise IV
Spirometer difference	51.4 cm.	69.9 cm.	77.7 cm.	115.8 cm.
Total ventilation	71.5 liters	97.2 liters	107.9 liters	161.0 liters
Total ventilation per square meter	36.1 liters	49.1 liters	54.5 liters	81.3 liters
$\frac{\text{Ventilation}}{\text{Vital capacity}}$	18.7 liters	25.4 liters	28.2 liters	42.1 liters
Ventilation index $\frac{\text{Ventilation}}{\text{Vital capacity}} \times 1 + \frac{\frac{\text{Ideal weight}}{\text{Actual weight}}}{2}$	16.8 liters	22.9 liters	25.4 liters	37.9 liters

The Ventilation Index in Patients with Various Diseases.—The Ventilation Index in Subjects with Cardiac Neurosis: Six persons were studied. All of them had symptoms referable to the heart without

TABLE 11.—*The Ventilation Index in Patients with Cardiac Neurosis*

	Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I		Exercise II		Exercise III		Exercise IV		Comment
					Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index	
♀	R. L. M.	66.0	121	1.92	31.8	17.2	42.0	22.7	47.5	25.7	70.6	38.0	Objective distress + with exercise IV; subjective dyspnea ++ with exercise IV and + with III
♀	L. S.	60.0	115	1.90	38.6	19.0	42.4	20.8	44.9	22.0	69.6	34.2	Objective distress + with exercise IV; subjective dyspnea + with all exercises
♂	E. U.	73.5	138	2.88	41.2	16.7	45.1	18.2	48.3	19.6	77.2	33.6	Subjective and objective distress + with exercise IV
♀	A. L. B.	63.0	110	1.94	31.0	16.3	39.5	20.8	42.8	22.5	65.3	34.4	Subjective and objective distress + with exercise IV
♀	K. H.	65.5	122	1.85	33.9	18.7	44.8	24.7	51.1	28.2	....	....	No objective distress; subjective distress + with I; ++ with II and III; refused to do exercise IV
♀	E. M.	65.0	102	2.03	31.5	17.7	46.0	25.2	....	....	....	....	No objective distress; subjective dyspnea ++ with both exercises; refused to do exercises III and IV

TABLE 12.—*The Ventilation Index in Patients with Early Cardiac Disease*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I		Exercise II		Exercise III		Exercise IV		Dyspnea	Comment
				Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index	Ventilation per Square Meter, Liters	Ventilation Index		
F. B. S.	64.0	109	1.98	37.2	19.8	45.8	24.3	54.4	28.9	74.7	39.6	III + IV +	Aortic insufficiency; ? rheumatic; no cardiac enlargement
J. H.	64.0	130	1.93	40.7	20.3	49.3	24.6	59.8	29.8	87.0	43.3	IV +	Patent ductus arteriosus; no cardiac enlargement or symptoms; swims; plays tennis
A. C.	64.5	117	2.04	40.8	20.5	51.3	25.6	....	....	98.2	49.1	IV ++	Patent ductus arteriosus; no cardiac enlargement; no cardiac symptoms; athlete
D. G. C.	67.5	126	2.34	51.5	24.2	57.7	27.2	....	....	....	....	II +	Hypertension; arteriosclerosis; slight cardiac hypertrophy; no cardiac symptoms
L. C.	58.0	130	1.09	44.2	34.5	58.4	45.5	....	....	....	....	I +	Hypertension; cardiac hypertrophy
V. B. M.	65.0	88	1.93	39.2	24.7	48.9	30.6	56.5	35.4	80.6	50.7	IV +	Hypertension; slight cardiac enlargement
H. F.	69.5	140	2.32	60.1	28.0	66.8	31.1	71.1	33.0	85.5	39.9	III + IV +	Rheumatic; myocarditis; no cardiac enlargement
V. O. V.	61.0	145	1.40	41.2	25.3	49.1	30.1	63.7	39.2	....	....	III +	Hypertension; slight cardiac hypertrophy
M. L. S.	64.5	128	1.45	33.7	22.7	42.0	28.3	50.6	34.1	82.0	55.3	III + IV ++	Cardiac hypertrophy, cause unknown; paroxysmal auricular flutter
R. O. E.	71.0	163	2.09	40.6	19.9	54.1	26.5	....	....	....	....	II +	Cardiac hypertrophy

demonstrable cardiac abnormality by physical, roentgenologic or electrocardiographic symptoms. Their vital capacities and their ventilation per square meter were within normal limits. For exercise I, their ventilation indexes were all below 20, and for exercise III and IV, were below 30 and 40, respectively. For exercise II, only 1 subject showed an index above 25.

Mention may be made of certain clinical features that were noted in connection with the tests in these subjects. The disproportion

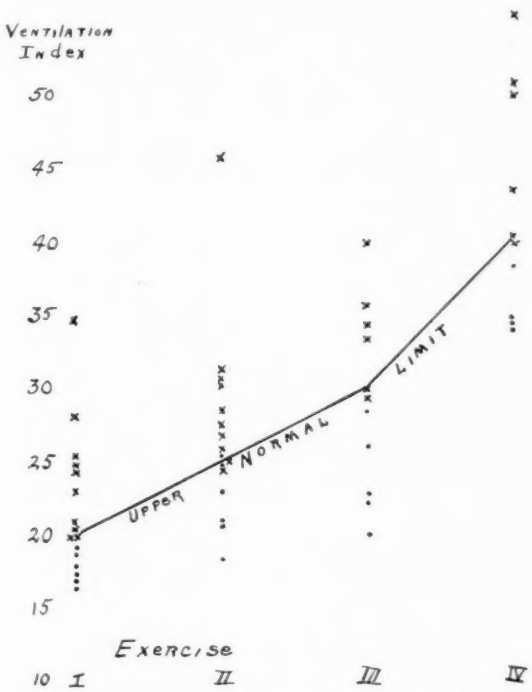

Fig. 3.—With very few exceptions the indexes for ventilation for the various exercises are at or above the upper normal limit in subjects with early cardiac disease (crosses) and at or below the upper normal limit in subjects with cardiac neurosis (dots).

between the apparent and the subjective distress was sometimes striking. However, we do not believe that these patients were malingering, but that they actually felt more dyspneic than did normal subjects under the same conditions. Another interesting feature is the fact that 2 of the 6 subjects refused to complete the test. No other patient has done this; even those with advanced cardiac disease have been willing to do

what they were asked to do, although subjects with cardiac decompensation have not, of course, been requested to perform any but the mildest exercises.

The Ventilation Index in Subjects with Early Cardiac Disease: Ten persons were studied. These patients had conditions representing various types of organic cardiac disease in the earliest stages in which a definite diagnosis could be made. Several of them had no cardiac symptoms, and several had no cardiac enlargement ascertainable by physical or by roentgen examination. None of them had ever had congestive failure. Their vital capacities were normal in 7 instances and reduced in 3. Their values for ventilation per square meter (table 12) were increased as compared with those of the normal subjects (table 2) in about half of the cases. The ventilation indexes were distributed as

TABLE 13.—*The Ventilation Index in Subjects Who Had Previously Had Congestive Cardiac Failure*

				Exercise I			
Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	Comment
R. B.	65.5	105	1.74	49.3	+	32.9	Syphilitic aortic insufficiency; one "break"
E. G.	66.0	118	1.57	49.2	+	34.4	Syphilitic aortic insufficiency; three "breaks"
W. C.	70.5	148	1.82	62.0	+	36.3	Hypertension; four "breaks"
W. S.	67.5	135	1.85	40.6	0	22.5	Hypertension; one "break"
T. R.	70.0	133	2.64	80.6	+	33.5	Hypertension; aortic insufficiency; four "breaks"
J. A.	66.0	118	1.78	60.2	0	37.3	Auricular fibrillation; four "breaks"

follows: (*a*) just below the upper normal limit, 1 case; (*b*) at the upper normal limit, 1 case; (*c*) above the upper normal limit, 8 cases. From these data it seems clear that the great majority of patients with even very early cardiac disease have an increased ventilation index.

In figure 3 the ventilation indexes of these patients are compared with those of persons with cardiac neurosis. The difference is striking. A few borderline values were obtained, but this is to be expected when one is dealing with disease in very early stages.

The Ventilation Index in Subjects with Congestive Cardiac Failure: In table 13 are shown observations in 6 cases in which there had previously been decompensation, but in which there was compensation when the test was performed. For exercise I, 5 of the 6 subjects had values above 30 for the ventilation index (average normal, 17.4; upper normal limit, 20). The sixth subject had a value only slightly above normal. He had had only one "break" in compensation; most of the others had had several "breaks."

The results in subjects with congestive cardiac failure at the time of the test are shown in table 14. The vital capacity was decreased, and the ventilation per square meter was increased in every instance. The ventilation indexes were greatly increased. A comparison of tables 13 and 14 indicates that the ventilation index is a more accurate measure of the patient's state than is the vital capacity. Four subjects (T. R., J. A., W. C. and W. S.) are listed in both tables. In each of them the ventilation index changed more with the restoration of compensation than did the vital capacity.

The prognostic value of the ventilation index is shown in figure 4. In the patient who improved, the ventilation index steadily decreased; whereas, a rising ventilation index occurred in the subject who died. Changes in body weight and in vital capacity are also plotted. In these

TABLE 14.—*The Ventilation Index in Subjects with Congestive Heart Failure*

				Exercise I			
Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	Comment
T. R.	70.0	144	1.94	85.2	+++	47.3	Hypertension; aortic insufficiency
J. A.	66.0	131	1.48	89.6	+++	53.0	Auricular fibrillation
S. W.	60.0	233	1.07	55.4	++	37.3	Hypertension; aortic insufficiency
S. P.	64.0	151	1.48	52.0	++	35.1	Hypertension
M. G.	62.0	180	1.15	60.7	++	52.8	Hypertension
W. C.	70.5	168	1.44	72.4	++	49.8	Hypertension
W. S.	67.5	147	1.62	47.6	+	29.7	Hypertension
J. U.	69.0	139	1.20	60.7	+++	50.6	Hypertension; emphysema
R. C.	66.0	127	1.60	70.6	++	46.4	Rheumatic, aortic and mitral endocarditis

subjects the vital capacity was of no prognostic value. The body weight paralleled the ventilation index in one subject, but not in the other.

(In patients with cardiac insufficiency only the data for exercise I have been presented. In most of the instances this was the only exercise performed, because the patient was too short of breath to do more. However, a number of these patients performed exercise II as well. As the results are entirely in accord with those obtained from exercise I, being at a corresponding but higher level, they are not presented. Patients with moderately or far advanced cardiac disease were never requested to perform exercise III and IV).

The Effect of Respiratory Obstruction: Experiments have been carried out on normal subjects under a number of different conditions and on patients with various diseases, and the general principle that $\frac{\text{ventilation}}{\text{vital capacity}}$ =degree of dyspnea has seemed to hold true in all instances except in subjects with respiratory obstruction (patients with cardiac neurosis are also an exception if one accepts their statement as to dyspnea, but not if the objective evidences are relied on).

Respiratory obstruction was produced in two normal subjects by inserting corks with holes of 4 mm. in diameter into the inspiratory and expiratory valves. As can be seen from table 6, these subjects suffered from considerably more than their usual respiratory distress in performing the various exercises. Although the dyspnea was greater, all the values for ventilation per square meter and for $\frac{\text{ventilation}}{\text{vital capacity}}$ were lower than when these subjects performed the same exercises under normal conditions. Therefore, it is evident that respiratory measure-

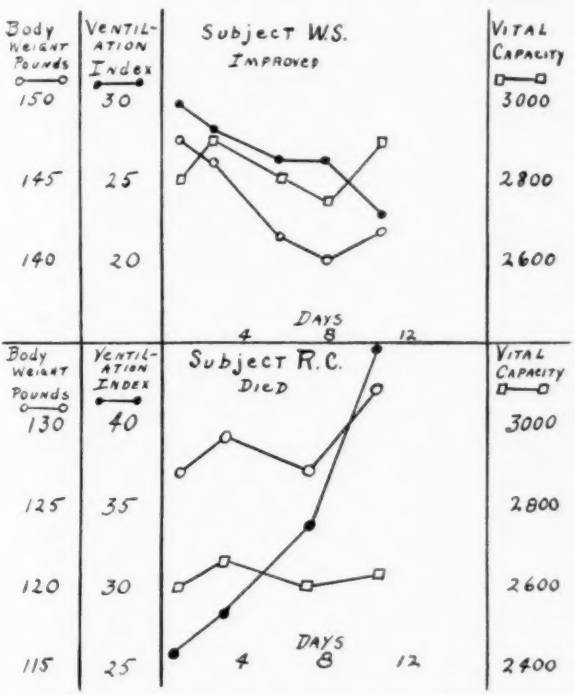

Fig. 4.—Ventilation index in two subjects. In neither subject was there a striking change in the vital capacity. Improvement was associated with loss of weight and diuresis in W. S., but there was no constant tendency for R. C. to gain weight as he became worse. In both subjects the change in weight was relatively slight. The direction of the change of the ventilation index was a reliable prognostic guide in both cases.

ments such as those we have carried out furnish a misleading index to the degree of dyspnea in subjects with respiratory obstruction.

The Ventilation Index in Subjects with Hyperthyroidism and in Subjects with Anemia: As can be seen from table 15, patients with

TABLE 15.—*The Ventilation Index in Patients with Hyperthyroidism and in Patients with Anemia*

Subject	Height, Inches	Weight, Pounds	Vital Capacity per Square Meter, Liters	Exercise I			Exercise II			Exercise III			Exercise IV			Comment
				Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	Ventilation per Square Meter, Liters	Dyspnea	Ventilation Index	
A. P.	64.0	123	1.72	40.5	0	25.2	78.3	+	48.8	93.4	++	58.2	....	..	....	Hyperthyroidism; basal metabolic rate + 50
A. H.	66.0	113	1.58	36.2	0	24.6	46.7	0	31.8	51.7	+	35.2	71.0	++	48.3	Hyperthyroidism; basal metabolic rate + 35
D. A.	68.0	142	2.11	43.8	0	21.4	58.2	+	28.5	....	..	....	....	..	....	Secondary anemia; hemoglobin 40
R. L. K.	61.0	93	1.80	47.3	0	28.0	51.1	0	30.2	56.8	+	33.5	....	..	....	Secondary anemia; hemoglobin 50
R. A.	65.0	105	1.99	40.8	0	22.4	45.1	0	24.7	56.6	+	30.1	72.5	+	39.9	Secondary anemia; hemoglobin 52

hyperthyroidism and anemia showed values somewhat above the normal. This was to be expected in hyperthyroidism as this disease when of severe degree may be considered as being always associated with early cardiac disease. The patients with anemia showed hemoglobin values of 50 or below. No cases of mild anemia were studied. Although, according to Cabot,[4] severe anemia may be associated with cardiac enlargement, none of our 3 cases showed evidence of this. It seems likely that severe anemia per se causes an increase in the ventilation index. If the test is to be used to detect cardiac disease, it is evident that one must first be certain that the patient is not anemic.

COMMENT

From the data that have been presented, it seems clear that when there is no obstruction to breathing, subjective respiratory distress (dyspnea) on exertion is dependent on three factors. These are: (1) the volume of the ventilation; (2) the vital capacity, and (3) the sensitiveness of the psyche. The third factor is unimportant except in neurotic persons. It is evident that, as Peabody pointed out, one feels short of breath when his breathing is greater than a certain fraction of his maximum ventilation.

The actual dyspnea is dependent not only on the presence or absence of disease of the various organs concerned in internal and external respiration, but also on the nutritional status. By means of appropriate correction, however, it is possible to eliminate more or less from consideration differences in nutrition and to obtain figures which are somewhat proportional to the degree of functional alteration of the heart or other portions of the respiratory-circulatory apparatus. However, it should be noted that the actual distress and the actual respiratory measurements were the same in obese persons with normal hearts as in subjects with early cardiac disease and normal nutritional status. This fact indicates the great importance of reducing the weight of obese patients with cardiac conditions.

We believe that the ventilation index affords a fairly accurate objective answer to the question: "How short of breath are you?" For this reason it seems a better guide to cardiac function than other tests that have been devised. It seems probable that the test will be of some value in measuring the effect of various therapeutic measures, such as the administration of digitalis, in patients with different types of cardiac disease in various stages of development.

The question arises as to whether, aside from research, the measure is of practical value. Our experience with the test is not yet sufficiently

4. Cabot, Richard C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926, p. 470.

broad to allow any certain answer to this question. The observations that have been reported for patients with cardiac neurosis and for those with very early cardiac disease suggest that the method may be of some diagnostic as well as prognostic value. Studies along this line are in progress.

SUMMARY

1. A series of standard exercises has been described during and after which the ventilation was measured.

2. Dyspnea is directly (but only roughly) proportional to the ventilation per square meter.

3. Dyspnea is inversely proportional to vital capacity, but again the agreement is rough.

4. The degree of dyspnea is fairly closely proportional to the expression: $\frac{\text{ventilation}}{\text{vital capacity}}$.

5. The actual dyspnea is greater in obese subjects and often less in very thin subjects than in persons of normal nutritional status. The expression: $\frac{\text{ventilation}}{\text{vital capacity}} \times \left[\frac{1 + \frac{\text{ideal weight}}{\text{actual weight}}}{2}\right]$ has been denoted as the ventilation index and the values for this are relatively independent of the nutritional state.

6. The ventilation index is usually normal in subjects with cardiac neurosis.

7. The ventilation index is usually slightly above normal in subjects with early organic cardiac disease, and is very much above normal in patients who have or who have had congestive failure.

8. The ventilation index is also increased in persons with diminished vital capacities from pulmonary disease, in subjects with hyperthyroidism and in patients with severe anemia.

9. The test is useless and actually misleading in persons with respiratory obstruction.

THE STAFF COUNT

ITS IMPORTANCE IN ACUTE INFECTIOUS DISEASE *

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The publications of Arneth in 1904 came as the result of the impetus given to the study of hematology by the introduction of Ehrlich's blood stains. Up to his time morphologic studies had been more or less limited to hematologic conditions. While studying the nuclear structure of the neutrophils in infection, Arneth [1] found that there seemed to be a constant relationship between the severity of the infection and the number of nonsegmented neutrophils. If the infection was very severe, neutrophils with three, four or five-lobed nuclei would disappear, to be replaced by others with nonsegmented nuclei. With the abatement of the infection, the nonsegmented neutrophils would rapidly be replaced by the mature forms. His later observations on the other leukocytes, though painstaking and correct, never received confirmation. Even his neutrophilic subclasses, though widely employed over an extended period of time, were never universally adopted. Schilling,[2] finding this classification cumbersome and impracticable, offered the same information in a simplified and more practicable formula. Instead of the numerous subclasses of neutrophils that depended on the shape and number of nuclear segments, he combined all of the segmented forms into one group called the segmented, and all of the nonsegmented into "jungkernige" and "stabkernige." The "stabkernige" form was an immature neutrophil, the nucleus of which, though nonsegmented, was thin and assumed many forms. The "jungkernige" form, however, usually was sausage-shaped and showed no indication of oncoming segmentation. Furthermore, instead of separately classifying 100 neutrophils, he included them in the differential count.

Since the appearance of my preliminary report in 1927 [3] on the newer hematologic aspects of the neutrophils in infection, the study of the morphologic structure of the leukocytes has been continued. During the past five years, about 20,000 blood smears taken from patients with

* Submitted for publication, Dec. 3, 1930.

* From the Hematological Laboratory of Beth Israel Hospital.

1. Arneth, cited by Klinkhardt: Qualitative Leukocytose, 1920, vol. 1, p. 2.

2. Schilling, V.: Das Blutbild und seine klinische Verwertung, ed. 4, Jena, Gustav Fischer, 1924, vol. 3; Biologische Leukocytenkurven, Deutsche med. Wchnschr. **50**:1583, 1924.

3. Weiss, Arthur: Am. J. M. Sc. **174**:45 (July) 1927.

a large variety of medical and surgical infections were examined. Complete examinations of the blood were carried out daily in most cases. When deemed necessary, examinations were made even more frequently. These blood counts were usually taken between 9 and 11 a. m., and were timed so that tests were usually obtained from the same patient at the same time. Blood films were stained according to the Jenner-Giemsa method, and a differential count of 200 or 300 cells was usually performed.

The following cases demonstrate the employment of this formula.

REPORT OF CASES

CASE 1.—G. S., a woman, aged 21, was admitted to the medical service of Beth Israel Hospital on Jan. 10, 1929, complaining of cough, fever and pain in the right side of the chest. She had gone to bed complaining of lassitude and slight headache, and was aroused from a deep slumber because of a sudden, sharp, lancinating pain in the right side of the chest. She found that she had fever, and that she breathed with difficulty.

On physical examination, the patient appeared to be acutely ill. Examination gave negative results except for local signs in the chest. There were fine, moist, intrapulmonary râles and pleural friction sounds. There was a diminished and distant respiratory murmur over the right side of the chest anteriorly. Breathing was bronchovesicular. Four days later, tubular breathing was elicited over the right side of the chest, anteriorly and posteriorly. The heart sounds were regular, although somewhat distant. On admission, the temperature was 105.4 F.; the pulse rate, 128, and the respiratory rate, 30. During the patient's illness, the pulse rate rose to 150. She was critically ill and toxic for one week, and the prognosis seemed poor.

Urinalysis revealed a specific gravity of from 1.010 to 1.036, a trace of albumin and a few white blood cells. A roentgenogram of the chest showed consolidation at the base of the left lung; there was compensatory emphysema of the left lung.

This patient had lobar pneumonia and clinically was very toxic. As the toxicity started early in the disease and increased as the disease progressed, the prognosis seemed extremely poor. From table 1 it can be seen that whereas the white blood cells were but slightly increased, the percentage of neutrophils, especially that of the staff cells, was high (70 per cent). In spite of the extreme toxicity, repeated examinations of the blood soon showed, by means of a gradual drop in the percentage of staff cells, that the patient would recover. Figure 1 shows the parallel rise and descent of the curves for the neutrophils and the staff cells. Another point of significance can be noted by examining the counts of January 11, 14 and 15. The total leukocyte count on these three days is of but slight significance. Although January 11 was the day preceding the high level of the staff count and January 15 the day showing a marked decrease in the staff count, all three days showed a neutrophil count above 90 per cent. If, therefore, one were to judge by the leukocyte and neutrophil counts, one would miss the evident action of the immature cells.

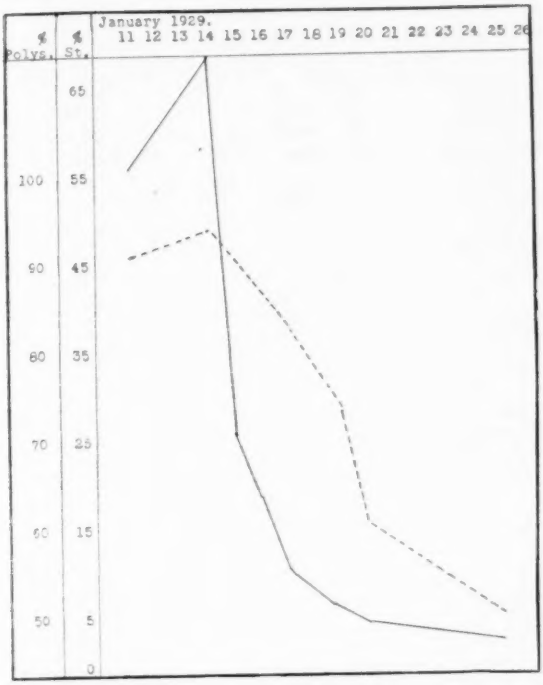

Fig. 1 (case 1).—Graph showing a sharp rise in the staff count before, and a decisive fall and return to normal after, the crisis. The percentage of polymorphonuclear neutrophils shows a similar though slower reaction.

TABLE 1.—*Results of Examinations of the Blood in Case 1*

Date, 1929	Erythrocytes, No. in C.Mm.	Hemoglobin, per Cent	Leukocytes, No. in C.Mm.	Total per Cent: Polymorphonuclears	Total per Cent: Mononuclears	Polymorphonuclear: Metamyelocytes	Polymorphonuclear: Staff Cells*	Polymorphonuclear: Segmented Neutrophils	Polymorphonuclear: Basophils	Polymorphonuclear: Eosinophils	Mononuclear: Segmented	Mononuclear: Monocytes	Comment
1/11	4,500,000	80	15,200	92	8	..	57	35	..	..	8	..	
1/14	4,000,000	65	10,200	95	5	..	70	25	..	..	5	..	
1/15	.....	..	16,200	91	9	..	27	64	..	..	8	1	Marked degeneration of neutrophils
1/16	.....	..	18,600	89	11	..	21	68	..	..	8	3	
1/17	.....	..	18,200	86	14	2	12	74	..	..	4	8	
1/18	.....	..	21,000	75	25	..	9	66	..	..	17	8	
1/20	.....	..	14,500	62	38	..	6	53	..	3	36	2	
1/25	.....	..	11,200	53	47	..	3	47	..	1	43	4	

* There was severe stimulation of the bone marrow, the staff cells rising as high as 70 per cent at the crisis. The number of leukocytes and the percentage of polymorphonuclears are of relatively minor importance.

Case 2.—I. S., a man, aged 41, was admitted to the hospital on Nov. 25, 1929, with the complaint of fever. He had been operated on for acute appendicitis on October 27. At that time general peritonitis and bronchopneumonia had developed. After a stormy course, his temperature had dropped, the wound had closed, and he had been discharged from the hospital as cured. During his first night at home his temperature rose to such a degree that a physician who was called advised his immediate return to the hospital. Thus, a week after his discharge he was readmitted, appearing pale but not otherwise ill. The abdominal wound was not completely healed, but in spite of tenderness over the area of the wound, it did not show abnormality. There were diminished resonance and voice sounds, with distant breath sounds over the lower lobe of the right lung below the level of the eighth rib. Above this level there was a small area throughout which the voice sounds were somewhat louder than normal. On admission, the temperature was 102.6 F., and during his stay in the hospital it rose as high as 104 F. A roentgenogram of the chest taken on November 26 showed mild congestion of both lungs, with interstitial changes in the base of the right lung, productive changes

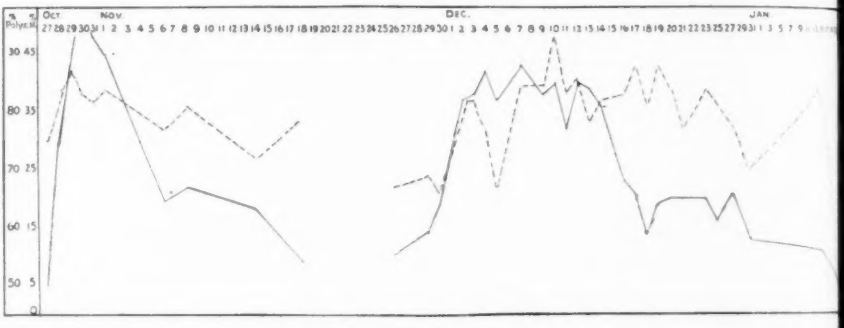

Fig. 2 (case 2).—Graph showing a precipitate rise in the staff count immediately after operation. The peak of the rise (54 per cent) was reached three days after operation; the count dropped to 9 per cent on the day of discharge. On readmission, there was a rapid rise in the immature cell count (43 per cent) within eleven days. The level remained high for one week and then gradually returned to normal.

at the roots of both lungs and generalized enlargement of the cardiac shadow. Repeated aspirations of the right side of the chest yielded some broken-down tissue and a small amount of fluid, examination of which showed streptococci. On December 6, a costal resection was performed and a subphrenic abscess was found. The abscess was drained, and 3 ounces of pus were evacuated. On December 18, thoracotomy was performed for empyema, and 30 ounces of fluid were evacuated. A smear of the thoracic fluid showed streptococci in long chains. Cultures of the blood repeatedly gave negative results.

Table 2 demonstrates that examination of the blood showed a slight reaction of the bone marrow. The examination performed the day after operation, however, showed a marked increase in the staff cells. The patient's postoperative course was extremely turbulent, the inma-

ture cells rising as high as 54 per cent. There was a concomitant decrease in the hemoglobin and the erythrocytes. The neutrophils showed marked toxic degeneration. Twenty-two days after appendec-

TABLE 2.—*Results of Examinations of the Blood in Case 2* *

Date, 1929	Erythrocytes, No. in C.Mm.	Hemoglobin, per Cent	Leukocytes, No. in C.Mm.	Total per Cent		Polymorphonuclear					Mononuclear		Comment
				Polymorphonuclears	Mononuclears	Metamyelocytes	Staff Cells	Segmented Neutrophils	Basophils	Eosinophils	Segmented	Monocytes	
10/27	5,150,000	80	10,400	75	25	..	5	70	..	..	18	7	
10/28	.....	..	16,000	84	16	..	30	54	..	..	12	4	
10/29	.....	..	18,200	88	12	1	42	45	..	..	8	4	
10/30	.....	..	12,000	83	17	..	54	29	..	..	15	2	Toxic degeneration of leukocytes
10/31	.....	..	13,000	82	18	..	48	34	..	..	14	4	Toxic degeneration of leukocytes
11/ 1	.....	..	13,000	84	16	..	45	37	..	2	16	..	Toxic degeneration of leukocytes
11/ 6	4,530,000	68	11,400	77	23	1	20	56	..	..	19	4	
11/ 8	.....	..	13,200	81	19	1	21	59	..	1	16	2	
11/14	.....	..	9,000	72	28	1	17	54	..	..	25	3	
11/18	4,500,000	68	7,800	78	22	..	9	59	..	..	20	2	Discharged
11/25	.....	..	.....	..	..	..	..	..	..	..	..	..	Readmitted
11/26	4,420,000	64	8,600	67	33	3	7	55	1	1	31	2	
11/29	4,380,000	69	9,400	69	31	2	12	55	..	..	28	3	
11/30	4,420,000	68	16,200	66	34	2	17	47	..	..	31	3	
12/ 2	.....	..	13,600	82	18	2	30	50	..	..	13	5	
12/ 3	3,980,000	68	9,000	82	18	3	34	44	..	..	15	3	One myelocyte
12/ 4	.....	..	8,200	77	23	5	37	35	..	..	19	3	One myelocyte
12/ 5	.....	..	12,000	67	33	5	32	30	..	..	29	4	Costal resection
12/ 7	.....	..	14,400	85	15	2	41	41	..	1	9	6	Toxic degeneration of leukocytes
12/ 9	.....	..	18,000	85	15	4	34	46	..	..	12	3	One myelocyte
12/10	.....	..	22,800	93	7	2	38	53	..	..	5	2	Toxic leukocytes, anisocytosis
12/11	.....	..	19,600	83	17	2	30	50	..	1	13	4	Toxic leukocytes
12/12	.....	..	16,400	85	15	2	38	45	..	..	10	5	Toxic leukocytes
12/13	.....	..	18,600	78	22	1	38	39	..	..	14	8	Platelets increased; slight macrocytosis
12/14	4,270,000	63	17,200	82	18	1	35	46	..	..	14	4	Platelets increased; slight macrocytosis
12/16	3,780,000	62	15,000	83	17	1	22	60	..	..	13	4	Anisocytosis; slight polychromatophilia
12/17	.....	..	12,400	88	12	1	20	66	1	..	8	4	
12/18	.....	..	10,800	81	19	..	14	67	..	..	14	5	Thoracotomy
12/19	.....	..	17,000	88	12	1	17	68	..	..	10	4	Platelets increased
12/20	3,300,000	57	13,800	84	16	1	18	65	..	..	12	4	Anisocytosis
12/21	.....	..	13,000	77	23	1	18	58	..	..	14	9	Polychromatophilia
12/23	.....	..	12,800	84	16	1	18	65	..	..	12	4	
12/24	.....	..	11,000	82	18	..	16	63	1	2	12	6	Platelets increased
12/28	3,410,000	62	10,000	77	23	3	17	55	1	1	20	3	
12/30	3,700,000	65	8,400	69	31	..	13	55	..	..	24	7	One myelocyte
1930													
1/15	3,780,000	69	16,400	84	16	..	11	72	..	1	11	5	
1/16	.....	..	16,200	76	24	1	9	64	..	1	22	2	
1/23	.....	..	7,800	46	54	..	6	38	..	2	50	4	One myelocyte

* The blood picture was normal except for a slight leukocytosis, which became much worse the day after appendectomy. The staff count held its high level until shortly before the patient's discharge. Immediately after readmission, however, the staff count started to rise and increased even after costal resection. At the time of the thoracotomy for empyema, the level of the staff cells had already started to descend.

tomy, the patient was discharged as apparently cured. Eight days later he was readmitted. The chart shows a gradual but progressive increase in the immature neutrophils during the first week after the second admission. Costal resection, which was performed on December 6, revealed

a subphrenic abscess. Examination of the blood on the following day showed a marked increase in the immature cells. Twelve days later thoracotomy was performed, and 30 ounces of pus was removed. At this time the blood picture showed a slow but progressive decrease in the immature neutrophils. Thirty-seven days after the thoracotomy, an examination of the blood showed a normal leukocyte count, a normal staff count and an increase in the lymphocytes. Figure 2 shows a precipitate rise in the staff cells and a gradual return to normal, with recovery. The second part of the graph shows the rapid rise and the sustained level of the staff cells for a period of three weeks. Costal resection apparently had no influence on the curve. Whereas the percentage of neutrophils was irregular and high, the staff count began its return to normal even before there were any signs of clinical improvement.

CASE 3.—I. M., a woman, aged 38, was admitted to the medical service of Beth Israel Hospital on April 22, 1930, with a condition diagnosed as acute diverticulitis. Her chief complaints were severe abdominal cramps, weakness, anorexia and dryness of the mouth and lips. Four days before admission, following her usual supper, the patient felt slight epigastric pain, to which she paid little attention. The continuation of this pain caused her to sleep poorly. In the morning, shortly after arising, she was seized with moderately severe abdominal cramps, and therefore did not eat breakfast or luncheon. In the afternoon she attended a clinic to have an infected finger dressed. On her way home, she was seized with an attack of severe, generalized, abdominal cramps, and barely managed to reach her home. She vomited soon afterward and had considerable gaseous eructation. The cramps continued irregularly for the next three days. Slight relief was obtained from an enema, which yielded a moderate fecal return. There were nausea, retching and gaseous eructation. During this time, the patient was under medical care and received a great deal of medication. She had had no bowel movements for three days before the onset of the illness. At no time had the patient noticed blood in the stools; she gave no history of chills, jaundice or melena. Because of the increasing weakness and anorexia, hospitalization was considered imperative. For many years the patient's diet had consisted mainly of vegetables and dairy foods. The bowels had always been sluggish, and purgatives had frequently been necessary.

Physical examination revealed the patient to be poorly nourished, anemic, sunken-eyed and dehydrated; she was lying in bed, moaning, and appeared acutely ill. Examination of the chest showed some dulness, with diminished breath and voice sounds over the base of the right lung in the axillary region. The abdomen was rounded and somewhat distended. Palpation revealed a slight generalized rigidity, which was probably a little more marked in the right upper quadrant. There was also generalized tenderness. In the right upper quadrant of the abdomen there was a resistance suggestive of an indefinite mass. The abdominal reflexes were not elicited. There was an infection of the distal end of the second finger of the left hand. A roentgenogram of the chest did not show consolidation or infiltration of either lung, pleural changes or deviation of the mediastinal contents. On admission, the temperature was 101.6 F.; the pulse rate, 112, and the respiratory rate, 30. During the week that the patient remained in the hospital, the temperature gradually rose to 104.5 F., the pulse rate to 150 and the respiratory

rate to 56. The urine showed albumin, a few granular casts, a moderate number of white blood cells and a few red blood cells. Cultures of the blood were repeatedly negative; the sedimentation rate was repeatedly as high as 68 per cent.

Table 3 shows that there were a moderate anemia and a marked increase in the number of leukocytes, with a marked increase in the neutrophils and staff cells. There was a concomitant decrease in the lymphocytes and monocytes. Perusal of figure 3 also shows that there was a sustained high level of the neutrophils and staff cells.

Repeated surgical consultations were invited, but the surgeons did not believe that a definite lesion of any abdominal viscera could be found. They therefore were of the opinion that the condition did not call for surgical intervention. The medical men, however, taking into

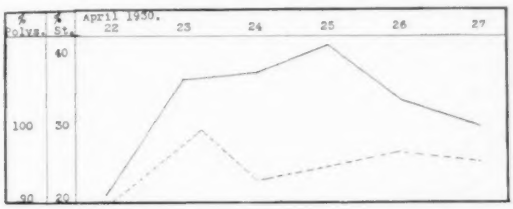

Fig. 3 (case 3).—Graph showing the curve of the staff cells and polymorphonuclears; there was no tendency to return from their elevated level to normal.

TABLE 3.—*Results of Examinations of the Blood in Case 3* *

Date, 1930	Erythrocytes, No. in C.Mm.	Hemoglobin, per Cent	Leukocytes, No. in C.Mm.	Total per Cent: Polymorphonuclears	Total per Cent: Mononuclears	Polymorphonuclear: Metamyelocytes	Polymorphonuclear: Staff Cells	Polymorphonuclear: Segmented Neutrophils	Polymorphonuclear: Basophils	Polymorphonuclear: Eosinophils	Mononuclear: Segmented	Mononuclear: Monocytes	Comment
4/22	.....	..	25,500	90	10	..	21	69	..	..	8	2	
4/23	3,920,000	72	17,600	98	2	2	34	62	..	..	1	1	
4/24	3,600,000	71	15,800	93	7	..	38	55	..	..	6	1	
4/25	3,420,000	71	20,800	95	5	2	40	53	..	..	4	1	
4/26	.....	..	21,500	97	3	2	32	62	..	..	3	..	One myelocyte
4/28	3,470,000	70	28,600	94	6	1	30	61	..	..	5	1	Two myelocytes; toxic degeneration of neutrophils

* In addition to a high leukocyte and polymorphonuclear neutrophil count, there was a high and progressively increasing staff count.

consideration the patient's history, the physical findings of a suggestive mass in the right upper quadrant of the abdomen, the laboratory observations of an exceedingly high rate of sedimentation and repeated examinations of the blood indicating pus, were of the opinion that a condi-

tion requiring surgical attention was present in the environs of the liver. The patient died, and a subhepatic abscess was found post mortem. In this case, the presence of a high staff count, which showed no tendency to decrease to normal, and the presence of physical signs pointing to disease in the right upper quadrant of the abdomen, should, I believe, have been sufficient to warrant operative intervention.

CASE 4.—C. S., a man, aged 50, was admitted to the hospital on Dec. 13, 1929. On admission, his chief complaint was pain in the left lower quadrant of the abdomen of twelve days' duration. Twelve days prior to admission, he had had a sudden attack of sharp, shooting pain in this region, occasionally radiating across to the opposite side of the abdomen. The pain was not related to the ingestion of food, exertion or posture. Accompanying these attacks of pain, his temperature had risen to between 101 and 103 F. During this period, the patient had had few intervals that were free from pain. During the attacks of pain, the abdomen had become swollen in the lower quadrant and tender to touch. After several days he had had slight pain on defecation. After proctoscopy the patient had passed a bloody stool. Pain in the left lower quadrant of the abdomen had persisted unabated. Eight days before admission, following an enema, the patient went into collapse. He had marked weakness, a rapid pulse, marked dyspnea and pallor. There was a history suggestive of a similar attack almost a year before admission, which stopped spontaneously after three or four days.

On physical examination, the patient was found to be well developed and moderately obese; he complained of pain in the left lower quadrant of the abdomen. He did not look acutely or chronically ill. The temperature was 99 F.; the pulse rate, 92, and the respiratory rate, 22; the blood pressure was 116 systolic and 80 diastolic. Examination of the chest gave negative results. There was a marked bulge in the lower part of the abdomen, particularly toward the left, with marked tenderness and slight rigidity over the entire abdomen. There was a large, palpable mass, mainly to the left of the midline, extending from 5 cm. above the umbilicus almost to the symphysis. Genito-urinary examination gave negative results. A roentgenogram of the colon showed no obstruction to the inflow of barium; the column passed rapidly to the cecum. There was spasticity of the sigmoid and the descending colon, with intermittent filling.

Urinalysis revealed: a specific gravity of 1.024, acetone of 3+, a few red blood cells, occasional white blood cells and occasional hyaline and finely granular casts. The rate of sedimentation was 15 per cent. Examinations of the blood on December 13 and 14 showed, respectively: red blood cells, — and 5,310; hemoglobin, — and 91; white cells, 65,000 and 66,200; metamyelocytes, 6 and 5; staff cells, 25 and 31; sigmented neutrophils, 57 and 53; basophils, 1 and 2; eosinophils, 0 and 4; lymphocytes, 2 and 4; monocytes, 1 and —, and myelocytes, 8 and 4. Toxic degeneration of the neutrophils was noticed at the first examination and marked anisocytosis at the second. The patient was operated on on December 14, and a large perisigmoid abscess was found. The sigmoid and small intestines were matted together and adherent to the peritoneum.

This case is of interest because it demonstrates that the blood picture is far more reliable in indicating the condition of a patient than his appearance. When I visited this patient before the operation, he sat in bed smoking a cigar, being barely inconvenienced by pain. No one who saw this man so comfortable and apparently healthy could have

believed that he would die on the following day because of a pathololgic process that he was harboring at that moment. However, an examination of the blood revealed the extreme seriousness of his condition.

CASE 5.—H. K., a woman, aged 61, was admitted to the ward at Beth Israel Hospital with a condition diagnosed as cholecystitis and cholelithiasis. Her chief complaints were abdominal pain and vomiting. The onset of symptoms had been sudden, with sharp, excruciating pain in the right upper quadrant, which radiated to the back. A few hours later she vomited some greenish fluid. A physician who was called in found the patient's temperature to be 101.2 F., and he prescribed medication to relieve the fever and pain. Three days later, on the day prior to admission, the patient experienced another attack. The temperature rose to 102 F., and hospitalization was advised. Fourteen years before, the patient had had "gallbladder trouble." She had had her last attack eleven years before. Although she had had no definite attacks since, she was never absolutely symptom-free. Her regimen had consisted of a lactovegetarian diet and of Carlsbad salts taken daily. She had never been jaundiced.

Physical examination revealed the patient to be acutely ill. The skin was moist and slightly icteric. There were a few scattered râles at the base of both lungs. Abdominal examination showed generalized tenderness, which was most marked in the right upper quadrant. Rigidity and tenderness of the right upper quadrant apparently covered a mass that seemed to extend to the umbilicus. On admission, the temperature was 104 F.; the pulse rate, 112, and the respiratory rate, 24. The blood pressure was 105 systolic and 70 diastolic. A roentgenogram of the chest showed the right side of the diaphragm to be elevated though freely movable. The urine contained albumin, 4+, and many white blood cells and granular casts; it was positive for bile. Surgical consultation was requested on the day of admission and the consultant advised observation.

Examination of the blood revealed: red cells, 4,340,000; hemoglobin, 80; white cells, 13,000; metamyelocytes, 6; staff cells, 27; segmented neutrophils, 47; lymphocytes, 14, and monocytes, 6; there was marked degeneration of the neutrophils.

Operation performed on the following day disclosed a large amount of bile in the peritoneal cavity and a ruptured gallbladder, with a stone in the gallbladder and in the cystic duct. With the blood picture showing 33 per cent of neutrophils, the patient should have received surgical care immediately.

COMMENT

What is the morphologic condition of the blood in acute infections, and what is revealed by a careful inspection of that mirror of physiologic and pathologic processes? Years ago it was taught that every infection resulted in leukocytosis and an increase in the polymorphonuclear leukocytes. To this was added the corollary that the higher the number of leukocytes, the greater was the patient's resistance against the invading organism, whereas the higher the percentage of neutrophils, the severer was the character of the infection. If the leukocytes were comparatively low in number and the percentage of neutrophils was high, the infection was supposed to have overpowered the patient's resistance, and usually terminated fatally. Thus, with the total value of the leukocytes as an index of resistance and the percentage of neutro-

phils as an index of infection, the part of all the other leukocytic elements was considered passive. Any increase or decrease in these cells was supposed to depend on a concomitant change in the neptrophils. The monocytes, considered by Ehrlich and Naegeli [4] as nongranular cells of myeloid origin, were believed to react biologically in direct proportion to any change in the neutrophilis. The lymphocytes, on the contrary, though passive, acted in indirect proportion to any change in the neutrophils.

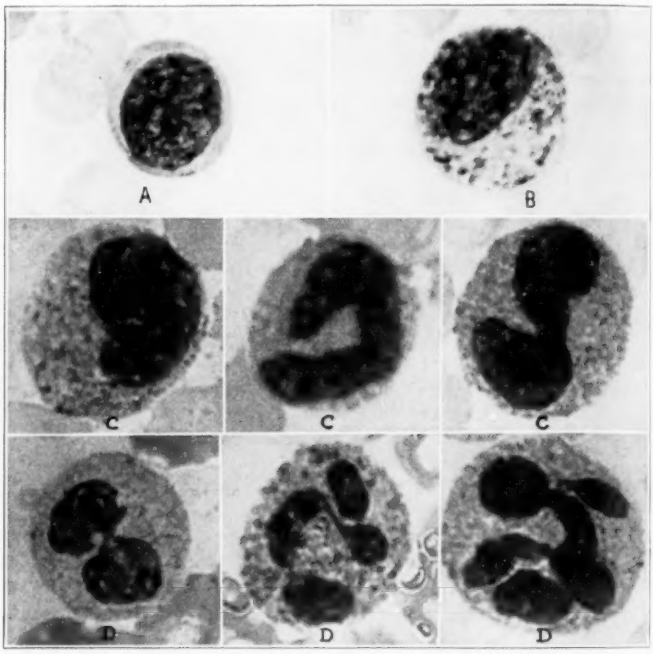

Fig. 4.—Photomicrographs of neutrophilic leukocytes: *A*, a myeloblast; *B*, a metamyelocyte; *C*, forms of staff neutrophils, and *D*, forms of segmented neutrophils.

As long as the interpretation of the observations of the blood in this series of cases was governed by these beliefs, numerous were the apparent discrepancies. Careful observations of numerous and serial examinations of the blood have encouraged the stand that although the neutrophils reflected in the blood stream in the course of any infection are an important unit in the reaction, they are not the sole active par-

4. Naegeli: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

ticipants. Instead of the invading agent, by means of its toxins, exerting a chemotactic force resulting in a neutrophilia, there is a definite chain of coordinated biologic components, each unit appearing on or leaving the center of the stage at a definite cue. As each cellular system is called on to act, the others almost automatically recede into the background, to reappear when necessary. Thus, the bone marrow, the reticulo-endothelial system and the lymphatic system are called into action.

The first system to be drafted into service with the onset of an acute infection is the neutrophil. The bone marrow, which has been steadily at work manufacturing its usual quota of segmented neutrophils (from 70 to 75 per cent) and nonsegmented or staff cells (from 3 to 5

TABLE 4.—*Classification of Infections According to the Percentage of the Staff Cells* *

	White Blood Cells	Neutrophils								
		Myelocytes	Metamyelocytes	Staff Cells, per Cent	Segmented, per Cent	Basophils, per Cent	Eosinophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	
Normal.....	From 5,000 to 9,000	..	..	3 to 5	60 to 70	0.5 to 1	2 to 5	20 to 30	4 to 8	
1. Mild.....	9,000	..	1	5	68	..	..	20	6	
2. Moderate...	10,200	..	2	10	67	..	..	20	1	
3. Severe.....	28,400	..	1	33	50	..	..	15	3	
4. Very severe.	36,400	..	..	41	47	..	..	10	2	Patient died
	13,000	..	..	79	17	..	..	4	..	Patient died
	4,000	..	..	50	17	..	..	24	..	Patient died

* The average blood pictures to be found in acute infections of varying severity are tabulated. As a rule, a severe infection will pass through all of the indicated stages from the height of the illness to the period of recovery. The three examples employed in the fourth phase died because of overwhelming infections.

per cent), is suddenly called on to furnish more cells. If the demand is mild, the bone marrow is able to increase its shipments, and there is a resultant increase in the leukocytes in the form of mature neutrophils. The nonsegmented or staff neutrophil may or may not be slightly increased. However, when the call on the bone marrow is too great for its normal productive forces, a moderate to marked increase in the staff forms occurs. This increase depends on the severity of the infection. Often at the crisis in a case of pneumonia, the staff cells may be as high as 70 per cent or more of the entire number of leukocytes. While this neutrophilic phase is in action, one observes that all of the eosinophils have left the circulation, that the monocytes are also gone or are present in very small numbers, and that the lymphocytes have decreased to from 1 to 10 per cent. With the surgical removal of the infectious focus, or the repulsion of the bacteria by the human host, the neutrophilic phase suddenly leaves the center of activity and is replaced

by monocytes. Though this cell was at one time believed to be of myeloid origin, because of its biologic reactions and supravital staining affinities, numerous investigators have agreed that it actually represents a definite cellular system of hematopoiesis. As a rule, the monocytes are showered into the blood stream at the moment the peak of the staff cells starts to recede. In chronic and subacute cases, however, the monocytes will be found in increased numbers until the period of convalescence. The monocytic phase is of short duration, and unless the blood is examined at frequent intervals during the crisis, this phase will be missed. The last system to be called into play is the lymphatic. The lymphocytes, which during the height of the infection drop from their normal percentage of between 25 and 30 per cent to between 1 and 10 per cent, gradually rise in number, and during convalescence will often be found to be present in numbers as high as from 50 to 60 per cent. That the increase in the various cellular elements at these different intervals of an infection is not a passive process, dependent on an increase or a decrease in the number of neutrophils, can be seen by the signs of marked hyperactivity of the monocytes and lymphocytes. Monocytes showing vacuoles, phagocytosed remnants and mitoses are often encountered. Lymphocytes also show their hyperactivity by the presence of Rieder forms, Türck irritation cells and double nuclei.

SUMMARY

A careful review of the data prepared from about 20,000 examinations of the blood performed during the past five years yields the following conclusions:

1. The leukocytosis caused by acute infections is primarily the result of stimulation of the bone marrow. This reaction of the bone marrow is a nonspecific, biologic phenomenon that depends not only on the type of organism, but on the degree of irritation caused by bacterial toxins. The neutrophilia thus brought about shows a varying percentage of immature or staff neutrophils, depending on the severity of the toxemia and the ability of the bone marrow to respond to it. A careful morphologic examination of serial blood films taken during the course of an infection will demonstrate that:

(*a*) The peak of the staff count and the height of the infection usually coincide.

(*b*) The peak of the staff count drops as soon as the infectious process is removed or overcome.

(*c*) The persistence of a high staff count usually means a complication.

(*d*) The persistence of a high staff count may mean that the infection is becoming subacute or chronic.

(*e*) The persistence of a high staff count without the possibility of removing the infectious focus usually indicates a fatal outcome.

(*f*) The presence of a high staff count early in the course of lobar pneumonia usually is indicative of a fatal outcome.

(*g*) The curve of the daily staff count is more accurate as an indication of the course of the infection than the chart of the temperature.

(*h*) The staff count is more reliable than the leukocytic or polymorphonuclear count.

2. Concomitant with the sharp drop in the staff count are a sudden increase in the number of monocytes and a return of the eosinophils into the circulation.

3. In subacute or chronic infections, one finds a persistence of an elevated staff count with an increased number of monocytes and lymphocytes.

4. Lymphopenia, which is present during the neutrophilic phase of acute infections, is replaced by lymphocytosis during the period of convalescence and healing. In subacute or chronic infections, the lymphocytes are usually increased.

For those who employ this method of morphologic examination of the blood, it is extremely important to bear in mind that a single report of a high staff count does not spell a fatal prognosis. (In case 1 the staff count rose as high as 70 per cent of the differential count, with eventual recovery.) Daily morphologic examinations of the cell are of inestimable importance, for it is on the curve that the prognosis of the case depends. It must be remembered that the changes in the blood are always to be considered conjointly with the complete clinical findings. It is also advisable to bear in mind that outstanding changes in the blood cannot be disregarded because of the lack of clinical corroboration. Nevertheless, it is also true that a definite clinical picture cannot be negated by a lack of confirmatory hematologic observations. Last, but not least, it must always be borne in mind that examination of the blood cannot always be employed as a means of diagnosis. Although one usually finds a definite biologic chain of leukocytic interreaction in infections, every now and then, owing to some unrecognizable cause, the blood picture fails to indicate the patient's condition. One must not forget that even now the reason for the appearance of the various cells in the circulation is not known, and therefore no cause can be ascribed for their failure to appear. These hematologic failures must not serve to discourage the clinician or the laboratory worker, but should spur him on to deeper and more exact observations. Careful serial morphologic examinations in which use is made of the neutrophilic subclasses are of inestimable value in the hematologic study of all infectious diseases.

UNEXPLAINED GASTRIC ANACIDITY*

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With the introduction of histamine as a stimulus to gastric secretion it became necessary to revise preexisting ideas about gastric anacidity, since it was found that many people who failed to secrete free acid after a meal of bread, gruel or alcohol gave a normal or nearly normal response after stimulation by the more powerful agent. In fact, total inability of the stomach to secrete acid now appears to be an uncommon condition, which is in contrast to the older observations that indicated that anacidity was to be found in from 5 to 40 per cent of people without obvious gastric disease.[1]

During the past few years we have studied the gastric secretion of about five hundred persons, with and without digestive symptoms, by means of the histamine test. Failure to produce free hydrochloric acid (when tested with dimethyl-amino-azobenzene) occurred in the following conditions: (1) invariably in cases of typical pernicious anemia; (2) frequently in cancer of the stomach, and (3) occasionally in the group of patients with diarrhea, anemia and stomatitis who may respond typically to feeding with liver as do patients with pernicious anemia. In addition to the aforementioned cases, anacidity has been present in a certain number of people with or without mild digestive symptoms, and for lack of a better term we have designated this condition as "unexplained anacidity." This article deals with this disorder.

Twenty-five cases of unexplained anacidity have been encountered. The frequency of this observation in relation to normal findings cannot be stated, as we were dealing with miscellaneous material. However, most of the "unexplained anacidities" were detected incidentally during routine tests and were not anticipated on the basis of the symptoms presented by the patient. Certainly the condition is an infrequent one.

Before classifying a case as "unexplained anacidity" every attempt was made to eliminate other clinical explanations. In no case was there sufficient evidence to make one consider seriously the diagnosis of pernicious anemia or cancer, and the patients were not sufficiently depleted

* Submitted for publication, Dec. 1, 1930.

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1. Keefer, C. S., and Bloomfield, A. L.: The Significance of Gastric Anacidity, Bull. Johns Hopkins Hosp. **39**: 304, 1926.

by febrile, malignant or other grave disease to allow one to infer a functional inhibition of proper secretion. Furthermore, in several cases repeated tests gave the same result. Gastritis is a tempting term with which to label obscure gastric disorders, and its possible relation to the present group of cases will be discussed later. However, none of the traditional causes that are alleged to lead to damage to the gastric mucosa were prominent in this series, namely, the excessive use of alcohol, hot or spiced foods or drugs.

Adequate solution of a problem such as the present one obviously depends on histologic study of the organ the function of which has been examined intravitam. But the difficulties are great when one considers the rarity of "unexplained" anacidity, and so far none of our patients have come to anatomic examination. There are no convincing data in the literature, since as yet no one has reported a series of this sort in which the histamine test has proved that an abolition of gastric secretion really existed.

THE CLINICAL PICTURE OF ANACIDITY

In view of the facts to be brought out by the analysis of our cases, it is necessary to mention briefly the symptomatology that has been associated in the literature with gastric anacidity. While every writer has recognized the latent occurrence of the condition, a certain group of phenomena have none the less been frequently attributed to it, especially diarrhea and mild symptoms of indigestion. However, in a hundred consecutive cases of acidity tested with the Ewald meal, Keefer and Bloomfield [1] were unable to detect characteristic symptoms, although doubtless their series was inadequate as histamine had not been used and in many of the cases the patients surely would have been capable of secreting freely under the more powerful stimulus.

METHODS AND MATERIAL

As pointed out, the present series consisted of miscellaneous hospital patients, most of whom did not have a primary digestive condition. The tests were done as a routine, and many of the subjects were selected to serve in determining normal standards of gastric function. In this group the discovery of anacidity was entirely unexpected.

The procedure [2] consisted of introducing a small tube into the stomach after the patient had fasted for at least twelve hours. The fasting secretion was withdrawn, and 0.1 mg. of histamine per ten kilograms of body weight was given hypodermically. The secretions were then aspirated over successive ten minute periods. As a rule, only a few cubic centimeters of mucoid material was obtained.

2. Bloomfield, A. L., and Polland, W. S.: The Diagnostic Value of Studies of Gastric Secretion, J. A. M. A. **92**:1508 (May 4) 1929.

RESULTS

In the accompanying table the main diagnostic facts of the series are summarized, but a number of points may be discussed in detail.

Age.—A consideration of the ages of the patients immediately throws light on one of the important problems of anacidity. Only two patients (cases 7 and 8) were under 40 years of age. The youngest patient in the series was 29 years old. It appears that anacidity is not as a rule purely congenital. Whether its development is due to external causes or whether some constitutional element enters in, cannot be said at present. This point will be studied further.

Clinical Diagnoses of Cases of Anacidity

Case	Age	Sex	Clinical Diagnosis
1	58	M	Tinnitus, congenital neurosyphilis
2	50	F	Migraine; psychoneurosis; undernutrition; anemia
3	42	F	Gas; constipation; indefinite abdominal pain
4	67	M	Arteriosclerosis; chronic prostatitis
5	75	M	Arteriosclerosis; myocarditis
6	65	M	Pulmonary tuberculosis
7	39	F	Psychoneurosis
8	44	M	Chronic arthritis; iritis
9	60	M	Arteriosclerosis; hypertension; spondylitis, glaucoma
10	55	M	Arteriosclerosis; hypertension
11	47	F	Psychoneurosis; dietary deficiency; acne rosacea; anemia
12	42	F	Psychoneurosis; drug addiction
13	44	M	Indigestion
14	62	M	Cholelithiasis
15	49	M	Erythema multiforme
16	40	M	Aortic insufficiency
17	56	F	Mucous colitis
18	29	M	Acne rosacea
19	45	M	Acute polyarthritis (convalescent)
20	60	M	Indigestion
21	67	M	Abdominal pain (unexplained)
22	48	M	Epilepsy
23	42	M	No disease
24	49	M	Chronic fibroid tuberculosis; indigestion
25	65	F	Indigestion

Sex.—There were eighteen men, and seven women, 72 and 28 per cent, respectively. However, more men than women come to the clinic, and more tests are made on men. It may be assumed that there is no great difference in sex incidence.

Familial History of Cancer, Stomach Trouble, Anemia or Neurologic Disorders.—Definite statements on these points were available in twelve cases. In no instance was the patient aware of the occurrence of the aforementioned disorders.

Occupation.—A miscellaneous group of occupations was represented, including housewife, barber, carpenter, cement worker, kennel caretaker, salesman, sheriff, surveyor, student, teamster and tailor.

Previous Diet.—Specific inquiries were made as to patient's dietary habits. In only one case (case 11) was there a suggestion of dietary

inadequacy. For the past three years this patient had subsisted largely on cereals and toast.

Alcohol, Drugs and Gastric Irritants.—There was no history in any case of excessive indulgence in or use of alcohol, drugs and gastric irritants, except in the following cases. In case 4 the patient had drunk 1 gallon (4.5 liters) of whisky daily until prohibition and none since; in case 9 the patient used to drink much whisky but had had none recently; in case 10 the patient drank from one to two glasses of wine with each meal; in case 21 the patient had drunk considerably many years previously. It seems most unlikely that any special factor of gastric irritation was of etiologic importance in these cases.

Gastro-Intestinal Symptoms.—A special study was made of gastro-intestinal symptoms, since it has been thought by some that a clinical association exists between gastric anacidity and diarrhea and indigestion. In regard to the movement of the bowels, twelve patients had normal habits, ten were habitually constipated and in only two was there an indication of abnormal looseness. In case 24 the patient had had frequent attacks of moderate looseness of the bowels in the last six years, and in case 4 the patient usually had from two to three movements daily. Fourteen, or 56 per cent, of the patients had never had indigestion or other gastric symptoms, and three, or 12 per cent, complained only of gas—a symptom so common in general practice as to have no special meaning. Definite gastric complaints were present in eight, or 32 per cent of the patients of this series: in case 2, periodic migraine with nausea and vomiting; in case 6, vomiting after the ingestion of large amounts of food; in case 9, the feeling that the stomach could not hold much; in case 10, a heavy feeling with gas, relieved by food; in case 13, gas and sour stomach; in case 17, an occasional indefinite abdominal pain and gas after meals; in case 25, gas and indigestion, and in case 11, a burning sensation in the stomach with belching.

In summary, the majority of these patients had no definite gastro-intestinal symptoms. The remainder presented a variety of mild complaints without specific characteristics and not essentially different from what one might encounter in persons with normal gastric secretion. It would be difficult to assume that the defect in gastric secretion per se produces definite symptoms, a conclusion that was reached by Bloomfield and Keefer in their previous study.

Evidences of Pernicious Anemia and Neurologic Changes.—Neurologic changes suggestive of the combined sclerosis of pernicious anemia were not detected in any member of the series, and from the standpoint of physical examination, there was no other evidence of pernicious anemia, such as smooth tongue or palpable spleen. The blood count

and blood picture were not unusual, except in two patients. In case 2 examination of the blood showed: red cells, 3,700,000; hemoglobin, 76 per cent; white cells, 6,200 with a low percentage of neutrophils (37 per cent). There was slight anisocytosis and poikilocytosis. Follow-up studies will show whether more definite change in the blood develops. In case 11 examination of the blood showed: red cells, 3,700,000; hemoglobin, 70 per cent; white cells, 5,700. The differential count and the morphologic characteristics were normal. The Wassermann test gave negative results in every case.

Roentgen Studies.—Roentgenograms of the gastro-intestinal tract were made in twenty cases; in nineteen cases nothing important was found. In case 20 there was an irregularity of the greater curvature extending from the cardia almost to the antrum. Cancer seemed unlikely because the whole stomach was flexible and freely movable.

Gastric Analysis.—In a previous paper,[3] we described the character and the composition of the gastric secretion in conditions in which there was a failure to respond to histamine such as cancer and pernicious anemia. The findings in the present series differed in no respect, and the material obtained from the stomach consisted of a few cubic centimeters of mucoid material which gave a yellow color on testing with dimethyl-amino-azobenzene.

Clinical Diagnosis.—One of the most important points under consideration was whether the gastric anacidity bore any real relationship to the patient's outstanding disease or whether it was an insignificant and incidental finding. The final diagnoses are given in the accompanying table. In sixteen cases (64 per cent) there seem to be nothing to explain the defect of gastric secretion. Five patients had mild digestive symptoms in no way different from those encountered in any hospital population; it cannot be said whether or not these symptoms were related to the anacidity, but it seems unlikely. In cases 2, 11, 20, 24 and 25 the patients had definite gastro-intestinal symptoms, and in case 25 the patient was relieved by hydrochloric acid.

COMMENT

It appears that failure to secrete acid (or indeed any actual gastric juice) occurs in a certain number of persons, apart from the well known associations of anacidity, such as pernicious anemia and cancer of the stomach. It may be estimated that such "unexplained anacidities" are encountered in from 3 to 5 per cent of the patients in a medical clinic. In the present series the disorder was distinctly one of middle

3. Bloomfield, A. L.; Roberts, A. M., and Polland, W. S.: The Composition of the Gastric Secretion in Cases of Anacidity, Tr. A. Am. Physicians **43**:242, 1928.

and old age, a finding which suggests that it is acquired rather than congenital, but beyond this no relation was found to age, sex, occupation, diet or habits. It has not been possible to define any symptom-complex that is clearly associated with the gastric disorder. This point deserves especial emphasis in view of alleged "anacidity diarrheas" and other syndromes that have been described from time to time. In the present series most of the cases were asymptomatic as far as the gastro-intestinal tract was concerned; in the few cases in which digestive symptoms occurred they presented no specific features. In only one instance was there evidence that the administration of hydrochloric acid may have had some beneficial effect.

The present report really sets the problem rather than answers it, and it remains to show the underlying lesion responsible for the disorder of secretion and the effect of the presence of complete anacidity on ultimate general health. A further question of special importance is whether anacidity of this sort is followed in a large percentage of cases by the development of cancer of the stomach, a point that has recently been raised again by Hurst [4] and by us.[5]

With these problems in mind, an "anacidity clinic" has been started. The patients are seen periodically; they are interviewed and examined, and roentgenograms and gastric analyses are made repeatedly. If any of the patients die, it is hoped that pathologic examination will be possible. At any rate a further report is planned after a sufficient interval, probably five or ten years, has elapsed.

4. Hurst, A. F.: The Precursors of Cancer of the Stomach, Lancet **2**:1023, 1929.

5. Polland, W. S., and Bloomfield, A. L.: Gastric Secretion in Cancer of the Stomach, Bull. Johns Hopkins Hosp. **46**:307, 1930.

METABOLISM IN PNEUMONIA

II. THE MECHANISM OF THE RETENTION OF CHLORIDE IN PNEUMONIA *

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Although the knowledge of a lessened concentration of chloride in the urine of patients with fever [1] seems to have antedated Redtenbacher's [2] report, he appears to have been the first to have definitely connected pneumonia with a regularly diminished excretion of chloride. Ever since then, the subject has attracted considerable attention. The original observations have been amply confirmed and extended.[3] Many studies on the metabolism of patients with pneumonia have been made, but, aside from the changes due to the increased protein catabolism, no change comparable to that in the excretion of chlorine (and sodium) has been observed, nor have these numerous investigations furnished a satisfactory explanation for the observed changes in excretion of the chloride.

One of the first hypotheses to have been advanced in explanation of this condition appears to be that of Traube,[4] who suggested that the low excretion of chloride was due to a failure of absorption from the intestine. This was shown to be false by Röhmann,[5] Terray,[6] Schwarz [7] and von Moraczewski,[8] who pointed out that the feces obtained during the period of diminished excretion of chloride in the

* Submitted for publication, Nov. 10, 1930.

* From the Littauer Pneumonia Research Fund, New York University.

* A preliminary report was read before the Society for Experimental Biology and Medicine, May 21, 1930.

* Read before the Section on Pathology and Physiology at the Eighty-Second Annual Session of the American Medical Association, Philadelphia, June, 1931.

1. Simon, J. F.: Animal Chemistry, translated by G. E. Day, London, 1846, vol. 2, p. 208.

2. Redtenbacher, W.: Ztschr. d. kaiserliche-königliche Gesellschaft d. Aerzte zu Wien **2**:373, 1850.

3. For a review of the earlier literature see Hutchison, R.: J. Path. & Bact. **5**:406, 1898.

4. Traube, L.: Symtome der Krankheiten des respiratorischen und circulatorischen Apparat, Berlin, 1867; quoted by Hutchison (footnote 3).

5. Röhmann, F.: Ztschr. f. klin. Med. **1**:513, 1880.

6. Terray, P.: Ztschr. f. klin. Med. **26**:346, 1894.

7. Schwarz: Wien. med. Bl., 1895, no. 49; quoted by von Hösslin: Deutsches Arch. f. klin. Med. **93**:404, 1908.

8. von Moraczewski, W.: Virchows Arch. f. path. Anat. **55**:11, 1899.

urine contained no more than the usual amounts of chlorine. There was, therefore, no failure of absorption or any abnormally large excretion of chloride into the intestine.

Schwenkenbecker and Spitta [9] collected and analyzed perspiration from a number of normal and febrile persons. In the one patient with pneumonia whom they studied, the amount of chloride in the perspiration was only a little more than that in the normal controls. The greatest amount of chloride was found in the profuse perspiration of patients with tuberculosis, and even then it was only 0.02 Gm. per kilogram of body weight greater than the normal amount. The chloride that disappears from the urine is, therefore, not to be found in the perspiration.

According to Terray,[4] Schwarz [7] and Hutchison,[3] the sputum of patients with pneumonia contains no more than about 0.5 Gm. of sodium chloride a day. Sunderman [10] found values up to 0.88 Gm. in some of his patients, but even this exceptional amount is not comparable to that which fails to appear in the urine. The reality of the retention of chloride in the urine must be regarded as established.

In fact, Redtenbacher,[2] in 1850, and Beale,[11] in 1852, believed this to be the case, and the latter regarded his analyses as establishing the fact of the retention of chloride in the pneumonic lung. That the pneumonic lung, because of its greater weight, does contain more chlorine than does the normal lung has been well established by the work of Terray,[6] Hutchison,[3] von Moraczewski,[8] Meillére [12] and Peabody,[13] but the amount so retained seems rarely to be more than 2 Gm., and is, as Hutchison pointed out, probably never more than 6 or 7 Gm. Since the total amount retained often greatly exceeds this, the amount contained in the consolidated lungs cannot, alone, account for the retention.

It was natural to look for the retained chloride in the blood. However, the results of numerous analyses, beginning with those of Runeberg [14] and Laudenheimer,[15] showed that the concentration of chloride in the blood of patients with pneumonia was not only not greater but was actually somewhat lower than that in the blood of normal persons.

9. Schwenkenbecker and Spitta: Arch. f. exper. Path. u Pharmakol. **56**:284, 1907.

10. Sunderman, F. W.: J. Clin. Investigation **8**:313, 1929.

11. Beale, L. S.: Tr. Med.-Chir. Soc., London **35**:325, 1852.

12. Meillère, M., reported by Achard, C., and Loepier, M.: Compt. rend. Soc. de biol. **53**:346, 1901.

13. Peabody, F. W.: J. Exper. Med. **17**:71, 1913.

14. Runeberg, J. W.: Deutsches Arch. f. klin. Med. **35**:266, 1884.

15. Laudenheimer, R.: Ztschr. f. klin. Med. **21**:513, 1892.

Hutchison was inclined to minimize the importance of this observation. He wrote:[16]

> The diminution of the chloride in the urine however, is out of all proportion to the degree of diminution found in the blood. In the latter it only amounts to a decigramme or less in every 100 cc. whereas in the urine the diminution may go to the length of total disappearance. It seems almost incredible that the kidney function can be so delicately adjusted that such a slight fall in the amount of sodium chloride in the blood should lead to an entire cessation of its excretion.

The conception of a threshold value for chloride in the urine corresponding to a concentration of chloride in the plasma below which no secretion into the urine would occur was apparently unknown to him.

The idea of a renal threshold for chloride as a definite concentration of chloride in the blood or plasma below which no excretion into the urine takes place was, it is true, overthrown by Aitken,[17] but his work definitely established the renal threshold as "a region in which the relation of renal excretion to plasma concentration changes rapidly," a conception that Hutchison regarded as "almost incredible."

But if the retained chloride is not present in the lungs or in the blood, where is it? It seemed likely that the muscles and liver, because of their bulk, might contain appreciable quantities. Also, since Padtberg[18] showed that in dogs the concentration of chloride of the skin was considerably increased after the intravenous injection of sodium chloride, it was possible that, in patients with pneumonia, also, some of the retained chloride was deposited in the skin. But analyses of muscle, liver and other tissues by von Moraczewski[19] and Hutchison,[3] and of the skin by Santini[20] and Peabody,[13] failed to show any appreciable accumulation of chloride.

It has frequently been suggested that the disturbance is not primarily in the metabolism of chloride but in that of water. It is supposed that, for some reason or other, water is retained and that sodium chloride is retained only in sufficient quantity to preserve the proper osmotic pressure and ionic equilibrium. That there may be a marked retention of water during pneumonia is unquestioned, for patients have been known to gain weight in spite of the marked loss of nitrogen. Accurate data on the extent of the retention of water are not plentiful; in fact, only Sunderman's data appear to be at all complete. He showed that even when the retention of water was most marked, as

16. Hutchison (footnote 3, p. 427).
17. Aitken, R. S.: J. Physiol. **67**:199, 1929.
18. Padtberg, J. H.: Arch. f. exper. Path. u. Pharmakol. **63**:60, 1910.
19. von Moraczewski, W.: Ztschr. f. klin. Med. **23**:483, 1897.
20. Santini, A.: Riforma med. **19**:477, 1903; quoted by Peabody (footnote 13).

in the case of his patient B_1, the maximum amount of chloride that could be so accounted for was only one third of the amount retained.

It is worthy of note that the retention of chloride generally continues for a few days after the crisis of the disease. The postcritical increase in the excretion of nitrogen, which is, in all probability, due to resorption in the lung, is much more prompt than the increase in excretion of chloride. It would seem that some of the chloride contained in the consolidated lung is transferred to other tissues. Finally, there comes a period of negative chloride balance. The assumption has been natural that this represents a return to the normal concentration of chloride in the unknown tissues that had previously been retaining chloride. However, it is usually found that this loss of chloride is not even as great as the amount retained while the patient was under observation, and that the negative balance is accompanied by diuresis and loss in weight. In other words, the postcritical loss of chloride seems due to that part of the previous accumulation that had accompanied the retention of water. The fate of the remainder of the chloride remains unknown.

Roehrich and Wiki [21] claimed to have observed a second rise in the retention of chloride from the twenty-fifth to the twenty-eighth day of the disease, after convalescence was well advanced. This interesting observation has not yet been confirmed by others.

Before proceeding to a discussion of my own experiments, it seems necessary to discuss in some detail two recent papers on the subject.[22] Wilder and Drake stated among their conclusions that:

> In infants with primary pneumonia we find a negative base and chloride balance if the intake of these ions is low, and a markedly positive balance if the intake is high.[23]

And Sunderman said:

> The present studies of the chloride balance do not support the view that pneumonia is characterized by a retention of chloride during the precritical period, but rather that it is characterized during the precritical period by a diminished capacity of the body to conserve chloride on a low intake of chloride and a diminished capacity to excrete chloride on a high intake of chloride. After the crisis the chloride balance becomes restored to normal from whichever deviation had earlier developed.[24]

These conclusions are in such striking agreement that, coming, as they do, from different laboratories, they carry weight. Nevertheless,

21. Roehrich, A. W., and Wiki, B.: Rev. méd. de la Suisse Rom. **20**:312, 1900.

22. Sunderman (footnote 10). Wilder, T. S., and Drake, T. G. H.: J. Clin. Investigation **7**:353, 1929.

23. Wilder and Drake (footnote 22, second reference, p. 363).

24. Sunderman (footnote 10, p. 329).

it is difficult to imagine how the metabolic disturbance in pneumonia can be so entirely different in patients receiving small amounts and in those receiving greater amounts of chloride. It would seem that the disturbance in metabolism must be the same in both groups.

Wilder and Drake presented the results of but one experiment on the metabolism of a child on a low intake of chloride. This was "nearly zero" or "zero."[25] Under such circumstances, it is not surprising that the child lost chloride. No other result could possibly have been expected. In five days, the total loss was 0.01425 equivalents, or 0.505 Gm. of chlorine. But, during these same five days, in spite of an apparent retention of 1,820 Gm. of water, the child lost 785 Gm. in weight. Assuming this loss to have been muscular tissue, it would have contained about 0.505 Gm. of chlorine.[26] The agreement is striking.

Wilder and Drake did not give data for the excretion of nitrogen. Calculations cannot be very wrong, however, if it is assumed that the loss of 785 Gm. in weight and the indicated retention of 1,820 Gm. of water were accompanied by the catabolism of approximately 2,600 Gm. of body tissue, containing approximately 1.6 Gm. of chlorine. This was as fully available for excretion as the same amount of chlorine ingested with food might have been. Since only 0.5 Gm. was excreted, it is obvious that approximately 1.1 Gm. was retained.

Sunderman reported data on the intake and output of nitrogen. All of his patients with pneumonia lost nitrogen and therefore catabolized body tissue. These tissues contained chloride, and, if this chloride was not found in the excretions, it was as truly retained as any chloride that might have been fed to the patient. In calculations on the retention of chloride, it is not sufficient to consider merely the body weight, as did Sunderman. It is conceivable that a patient might catabolize 1 Kg. of body tissue per day and retain an equal amount of water. The kilogram of body tissue would furnish about 0.7 Gm. of chlorine. If the intake of chlorine were 1 Gm. and the excretion 1.2 Gm., there would be an apparent loss of 0.2 Gm., whereas, in truth, there would be a retention of 0.5 Gm.

Examination of Sunderman's results indicates that something of this sort actually occurred. The seven precritical days on which he based his conclusions include one each in cases B_1 and B_2, two in B_3 and three in B_5. The losses of nitrogen on these days varied from 7 Gm. in a boy weighing 26.5 Kg. to 27 Gm. in a man weighing 61 Kg. It is difficult to calculate the exact amount of chloride correspond-

25. Wilder and Drake (footnote 22, text, p. 356 and table, p. 357).

26. Katz, J.: Arch. f. d. ges. Physiol. **63**:1, 1896. Magnus-Levy, A.: Biochem. Ztschr. **24**:363, 1910.

ing to this amount of nitrogen. According to Benedict,[27] in persons during fasting, there is a steady fall in the ratio of chlorine to nitrogen in the urine as the fast is continued. Moreover, particularly during the first days of the fast, this ratio varies considerably in different persons. Sunderman's studies were made on patients between the sixth and ninth days of the disease. At this time, the losses of nitrogen were, approximately, twice as great as those in normal persons during fasting. For the purpose of calculating the proper ratio of chlorine to nitrogen it might be urged that the ratio that obtains between the sixth and the ninth day of a fast in normal persons should not be taken, but, instead, that existing between the twelfth and the eighteenth day.

Reference to Benedict's compilation of the data on fasting persons shows that these are available only for his own experiment on L, and for four experiments on Succi. Of the latter, three show values

TABLE 1.—*Excretion of Chlorine and Nitrogen in Patients During Fasting* *

	Subject L.			Succi		
Days of Fast	Nitrogen, Grams	Chlorine, Grams	100 Chlorine / Nitrogen	Nitrogen, Grams	Chlorine, Grams	100 Chlorine / Nitrogen
12	10.13	0.31	3.1	7.88	0.405	5.14
13	10.35	0.32	3.1	3.86	0.230	5.96
14	10.43	0.26	2.5	5.87	0.119	2.05
15	8.46	0.16	1.9	5.66	0.137	2.42
16	9.58	0.14	1.5	6.05	0.113	1.87
17	8.81	0.12	1.4	6.78	0.130	1.91
18	8.27	0.15	1.8	6.00	0.258	4.30
Average	9.43	0.21	2.2	6.01	0.199	3.01

* Data from Benedict (footnote 27).

that are much higher than those in the fourth experiment (Florence). In order to secure minimal values, the data for Benedict's subject L and for Succi's fast in Florence are given in table 1. From these data, it is apparent that the minimal amount of chlorine that must have been derived from the catabolism of body tissue in Sunderman's experiments was 0.022 Gm., or 0.62 milliequivalents, per gram of nitrogen lost.

The pertinent data from Sunderman's tables for the seven pre-critical and the three critical days on which he bases his conclusions have been collected in table 2. The fourth column, giving the chlorine equivalent to the nitrogen lost, on the basis of 0.62 milliequivalents of chlorine for each gram of nitrogen, and the fifth column, giving the sum of this and the intake of chlorine as the total chlorine available for excretion, have been inserted. As is evident from the last column,

27. Benedict, F. G.: A Study of Prolonged Fasting, Washington, Carnegie Inst., 1915.

the balance was positive on every day but three, and on one of these the negative balance was small, 0.5 milliequivalents. In the other two instances, the negative balance was followed (B_4), or preceded and followed (B_5), by retentions of chlorine nearly sufficient to balance the losses.

In this calculation it is true that no account has been taken of the chloride that may have been lost in the perspiration. Sunderman mentioned that the highest value of sodium chloride per day that he actually observed was 0.27 Gm., although he regards this as almost certainly too low, because of faulty technic. He did not state whether or not this value was taken in a patient on a diet high or low in chloride or before or after the crisis of pneumonia.

TABLE 2.—*Recalculation of the Balance of Chlorine in Patients Observed by Sunderman*

Case	Nitrogen Lost, Gm.	Intake of Chlorine M Eq.	Chlorine Equivalent to Nitrogen Loss M Eq.	Total Chlorine Available for Excretion M Eq.	Output of Chlorine					Balance M Eq.
					Urine M Eq.	Feces M Eq.	Sputum M Eq.	Blood M Eq.	Total M Eq.	
B_1	13	17	8.0	25.0	0.2	2.5	5.1	3.0	10.8	+14.2
	16	17	9.9	26.9	0.0	...	11.6	4.6	16.2	+10.7
B_2	17	36	10.5	46.5	36.9	...	2.8	4.2	43.9	+2.6
B_4	27	22	16.7	38.7	39.5	...	....	5.0	44.5	−5.8
	26	25	15.5	40.5	31.6	0.6	1.8	1.8	35.8	+4.7
	27	25	16.7	41.7	37.6	...	1.0	3.6	42.2	−0.5
B_5	7	26	4.3	30.3	22.9	2.1	0.1	2.0	27.1	+3.2
	9	22	5.6	27.6	30.2	0.4	2.9	...	33.5	−5.9
	7	19	4.3	23.3	13.6	...	4.6	3.1	21.3	+2.0
	10	19	6.2	25.2	13.2	3.0	3.8	...	20.0	+5.2

Schwenkenbecker and Spitta,[9] whose work was cited by Sunderman, obtained, as has already been stated, values as high as 2.7 Gm. per day per hundred kilograms of body weight. However, this was in a patient with tuberculosis. The only patient with pneumonia studied by them excreted 0.73 Gm. per hundred kilograms of weight on the day before the crisis, 0.95 Gm. on the day of the crisis and 0.73 Gm. on the following day. For patients such as Sunderman's B_4 (heaviest in weight), an excretion of 0.73 Gm. of chloride per hundred kilograms of weight would be about 0.445 Gm., or 7.6 milliequivalents, per day. It is true that this is sufficient to turn the retentions into losses in every case but in B_4. But the calculations in the table have been based on the minimal value of 0.62 milliequivalents of chlorine for each gram of nitrogen lost. If the ratio of 1 milliequivalent per gram, which is lower than existed before the eighth day in any of Benedict's nine patients during fasting, is used, a retention of chloride would be indicated in every case.

Nothing has been said of Sunderman's consideration of the chloride found in the blood removed for analyses as part of the output of chloride. There is, in my opinion, little justification for such a consideration. This chloride was not excreted by the body, but was removed from it; it is scarcely any more to be included in the "output" than would the chloride content of a finger be, had it, instead of a corresponding weight of blood, been removed for analysis.

That there is something wrong with Sunderman's reasoning is apparent from a consideration of the results in patient B_1. On two successive days, this patient excreted 17 and 20 Gm. of nitrogen, resulting in a loss of 13 and 16 Gm. of nitrogen, respectively. On these two days, he excreted only 0.2 and 0.0 milliequivalents of chloride in the urine, and, in the urine and feces, a total of 2.7 milliequivalents. A more effective retention of chloride cannot be imagined. Nevertheless, according to Sunderman's method of calculation, it is impossible to decide whether there was a retention or a loss of chloride on these days.

There is, therefore, no reason to believe that the disturbance in chloride metabolism is any different in patients on diets low in chloride than it is in those receiving liberal amounts of salt. The nature of the disturbance remains unknown.

EXPERIMENTAL DATA

In view of the difficulties inherent in experiments on the metabolism of patients with pneumonia, and because it was desired to study changes in the early stages of the disease, it was decided to experiment on animals. The dog appeared to be the most suitable animal for our purpose. Lamar and Meltzer [28] had induced pneumonia in dogs by intratracheal insufflation of pneumococcus cultures. The necessity for anesthesia proved to be an undesirable feature of their technic, and, after a few trials, it was discarded in favor of intratracheal injections of a centrifugated culture. In some cases, a pneumococcus autolysate prepared by the method of Parker and Pappenheimer [29] was also injected. In one experiment, the inoculation was made directly into the lung. A culture of type I pneumococcus, extremely virulent for mice, was used throughout.

It was found that the dogs refused to eat after inoculation and that food previously ingested or given by stomach tube was vomited. It was therefore decided not to feed the animals after the experiment had begun, but to collect the samples of urine during, and for a few days after, the fever, then to feed the dogs double rations, to bring

28. Lamar, R. V., and Meltzer, S. J.: J. Exper. Med. **15**:133, 1912.
29. Parker, J. T., and Pappenheimer, A. M.: J. Exper. Med. **48**:695, 1928.

them back to their original weight, and, after several days on the standard ration, to repeat the experiment, sterile broth being used instead of the pneumococcus culture. The death of two of the animals made it impossible to carry out this program in full.

The content of nitrogen was determined by the method of Kjehldahl and that of chlorine by digestion of the urine with silver nitrate, nitric acid and a small amount of potassium permanganate, with subsequent titration of the excess silver nitrate.

PROTOCOLS

Dog 6, a female setter weighing 19 Kg., was kept on a diet consisting of 80 Gm. of dried meat residue (obtained from the Valentine Meat Juice Company), 70 Gm. of cracker meal, 10 Gm. of vitavose (a wheat-germ preparation made by

TABLE 3.—*Control Experiments. The Excretion of Nitrogen and Chlorine in the Urine After the Injection of Sterile Broth*

Experiment 31				Experiment 32			
		Chlorine				Chlorine	
Date	Nitrogen, Gm.	Gross Gm.	Net*	Date	Nitrogen, Gm.	Gross Gm.	Net*
3/1.....	7.93	0.883	.....				
3/2.....	9.45	1.320	.....	3/31.....	9.84	1.230	.....
3/3.....	9.71	1.070	.....	4/ 1.....	11.69	0.780	.....
3/4.....	7.94	1.080	.....	4/ 2.....	11.02	1.000	.....
3/5.....	2.05	0.179	0.091	4/ 3.....	4.35	0.368	0.277
3/6.....	5.19	0.411	0.383	4/ 4.....	1.83	0.402	0.360
3/7.....	2.56	0.220	.....	4/ 5.....	3.88	0.952	0.910
3/8.....	4.41	0.376	.....	4/ 6.....	5.10	0.502	.....

* This calculation was obtained by deducting the chlorine content of the broth injected into the animal.

E. Squibb & Sons), 20 Gm. of bone-ash, 60 cc. of maize oil, 1.50 Gm. of salt and 1,000 cc. of water. This animal was used for three experiments with pneumococcus cultures and for two control experiments. In order to facilitate discussion, the latter will be described first, though they were not, of course, the first to be performed. After the collection and analysis of the urine for four days during which the dog was kept on standard diet, food was withheld. On the first day of the fasting, March 5, 10 cc. of sterile broth was injected intratracheally at 10:20 a. m. The rectal temperature, which had been 101.7 at 8:50 a. m., was 101.5 when a second injection of 12 cc. of sterile broth was made at 1:20 p. m. The temperature was 101.7 at 2:30 and 102 at 4:30 p. m. On the following day, 17 cc. of sterile broth was injected at 9:15 a. m., and the temperature fluctuated between 101 and 101.7.

This experiment was followed by one in which a pneumococcus culture was used (experiment 63, table 4). After the animal had recovered his normal body weight, urine was again collected for a few days while the animal received the standard diet. Food was again withheld, and 20 cc. of sterile broth was injected intratracheally on April 3. This had no effect on the temperature. On each of

the following days, 10 cc. of sterile broth was injected, with the same lack of effect on the rectal temperature.

In experiments 61, 62 and 63, the same dog received cultures of a virulent type pneumococcus. The results of the analyses of the urine are summarized in table 4. The protocols of the individual experiments follow.

EXPERIMENT 61.—On February 11, a mixture of 5 cc. of pneumococcus autolysate and 5 cc. of a suspension of living pneumococci, each representing approximately 100 cc. of an eighteen hour culture, was injected intratracheally at 10:10 a. m. The temperature rose from 101.9 to 103 F. at 1 p. m., at which time 12 cc. of a suspension representing 150 cc. of a twenty-one hour culture was injected. At 3 p. m., the temperature was 105.4 F. and the dog was panting. Subsequent records of temperature and respiration, respectively, were 5:35 p. m., 107.5 F. and 75; 6:35, 106.4 and 66; 12 midnight, 103 and 50; 8:15 a. m., 102 and 22.

The following day at 9:30 a. m., 7 cc. of a suspension equivalent to 200 cc. of a sixteen hour culture was injected intratracheally. At 11 o'clock, the tempera-

TABLE 4.—*Excretion of Nitrogen and Chlorine in the Urine* *

Experiment 61				Experiment 62				Experiment 63			
		Chlorine				Chlorine				Chlorine	
Date	Nitrogen, Gm.	Gross Gm.	Net † Gm.	Date	Nitrogen, Gm.	Gross Gm.	Net † Gm.	Date	Nitrogen, Gm.	Gross Gm.	Net † Gm.
2/ 6	8.50	0.903	....	3/16	11.88	0.91	....	4/14	11.52	1.22	....
2/ 7	10.53	0.714	....	3/17	11.48	1.29	....	4/15	12.31	1.33	....
2/ 8	7.75	1.17	....	3/18	9.83	0.91	....	4/16	6.09	1.04	....
2/ 9	9.64	1.03	....					4/17	13.55	1.26	....
2/10	11.51	1.07	....								
2/11	6.40	2.64	2.54	3/19	4.04	1.00	0.91	4/18	3.70	1.24	1.19
2/12	4.63	0.29	0.26	3/20	4.97	0.27	0.20	4/19	4.58	0.11	....
2/13	7.00	0.071	....	3/21	3.88	3.88	0.28	4/20	7.02	0.44	....
2/14	6.11	0.029	....	3/22	2.54	0.32	....				
2/15	8.47	0.035	....	3/23	3.41	0.54	....				

* These experiments were performed on dog 6 in which a probable case of pneumonia was followed by recovery and in which subsequent inoculations produced but little effect.

† This calculation was obtained by deducting the chloride content of the culture injected into the animal.

ture was 102.4 F., and the respiratory rate was 50; at 12:10 p. m. they were 105 F. and 75, respectively; at 2, 106 and 80; at 4, 104.4, panting; at 5:30, 104, panting; at 9:30, 104.3 and 30 and at 8:30 a. m., 102 and 30.

EXPERIMENT 62.—At 10 a. m. on March 19, 12 cc. of a suspension equivalent to 300 cc. of a seventeen hour culture was injected into the dog intratracheally. There was no effect on the temperature until 1:20 p. m., when 8 cc., also equivalent to 300 cc. of a twenty hour culture, was injected. At 3 p. m., the dog had a severe chill, and the temperature was 102.4 F. This rose to 104.6 at 4:45, but fell to 103.4 F. at 6. p. m.

The next morning the temperature was normal, and the injection of 16 cc. of a suspension equivalent to 600 cc. of an eighteen hour culture was without effect on the temperature. The experiment was repeated on the following day, with the same lack of success. The temperature remained unchanged.

EXPERIMENT 63.—At 10:45 a. m. on April 18, 10 cc. of a suspension equivalent to 600 cc. of an eighteen hour culture was injected into the right lung of the same dog. At 12:45, the temperature had arisen from 100.6 to 104.8 F., the respiratory rate was 60, and the dog had a chill. The temperature was 105.2 F. at 2:20;

105.8 at 4; 105.4 at 5 and 104.4 at 6. The respiratory rate all afternoon was about 40 per minute. At 8:10 p. m. the temperature was 102.6, and at 11:40 it was 102.1 F.

In view of the apparent resistance of the animal to these large doses of pneumococcus culture, it was believed that the serum might show marked protective action. However, the usual tests on mice made by Miss Georgia Cooper of the Department of Health of New York City showed that this was not the case.

Experiment 5 (table 5).—A female collie, weighing 13 Kg., was fed a mixture of 20 Gm. of dried meat residue, 20 Gm. of cracker meal, 10 Gm. of vitavose, 15 Gm. of bone-ash, 30 cc. of maize oil, 1 Gm. of salt and 700 cc. of water. For several days, the rectal temperature fluctuated between 103 and 104 F., which was apparently normal for this dog. At 10:20 a. m. on February 11, a mixture of 5 cc. of a pneumococcus autolysate and 7 cc. of a fresh suspension, equivalent to 100 cc. of an eighteen hour culture, was injected into the trachea. At 11 o'clock the temperature was 104.3 F., but at 12 o'clock it had reached 105, and the dog seemed quite sick. The temperature continued to rise, reaching 105.9 at 1:30, 105.8 at 3 and 160.4 F. at 5:30 p. m. At this time the respiratory rate was 55 per minute. The temperature then fell slowly to 105.8 at 6:35 p. m., 104.8 at midnight and 103 F. at 8:15 a. m. Respirations continued to be rapid, the rate being between 50 and 58 a minute.

At 9:30 a. m., on February 12, the dog received 6 cc. of a suspension, equivalent to 200 cc. of a sixteen hour culture, intratracheally. The temperature rose slightly, reaching a maximum of 105.2 at 12 noon, and then declined, to remain at about 104 F. from 2 to 8:20 p. m. The respiratory rate increased, reaching 70 at 8:20 p. m. and 80 on the following morning. It remained at this level all day, although the temperature was only 103.8 F.

On February 14, the temperature varied between 102.5 and 103.8 F., but the respiratory rate increased from 100 in the morning to 130 in the evening. The dog coughed a great deal, and the muscles of the neck and front legs twitched.

At 1:15 p. m. on February 15, a laboratory attendant found the dog in convulsions. When I saw the dog, the convulsion was over; she was lying on her side, the temperature was 103.8 F., and the respiratory rate 85. At 6 p. m., the dog was standing up, staring at me without recognition, barking wildly and refusing to permit handling. After about five minus, she became quiet, lay down and permitted the insertion of the thermometer. The temperature was 103.6 F., the respiratory rate 75, and the pulse rate 150. On February 16, at 10:30 a. m., a convulsion suddenly developed, which lasted three minutes, and after which the dog was quiet. At 8 p. m., the temperature was 102.9 F., the respiratory rate 75 and the pulse rate 150. An attempt was made to feed the dog, and the pan was placed under her mouth. She made no attempt to take the food, but the muscles of the head began to twitch, then those of the neck were involved, and, in about a minute, the dog was in a tonic-clonic convulsion. The jaws were wide open at first, but then closed. The convulsion lasted for three minutes, after which the dog was quiet.

The condition did not appreciably change during the next day, the respiratory rate remaining at 80 or 90 and the temperature at from 103 to 104.5 F. The dog died during the night of February 18. At autopsy, the lungs showed only slight foci of consolidation. Nothing in the appearance of the heart or other organs gave a clue as to the cause of death. Pieces of the lung, medulla and cerebellum were fixed in formaldehyde and sent to Dr. Alexander Fraser, who reported intense congestion and bronchopneumonia in the lungs and slight meningitis, with foci of encephalitis in the cerebellum and medulla.

EXPERIMENT 7 (table 5).—A male mongrel, weighing 12.5 Kg., was fed a mixture of 45 Gm. of dried meat residue, 45 Gm. of cracker meal, 15 Gm. of bone-ash, 10 Gm. of vitavose, 1.50 Gm. of salt, 30 cc. of maize oil and 500 cc. of water. At 10:50 a. m. on April 3, a mixture of 10 cc. of a pneumococcus autolysate and 10 cc. of a fresh suspension, equivalent to 600 cc. of an eighteen hour culture, was injected into the trachea. The temperature rose from 100.5 to 103.3 F. at 12:30 p. m. and to 105.4 F. at 1:50. It continued at this height until 4:40 p. m., but by 11:50 p. m., it had fallen to 104.4 F. The respiratory rate was not greatly increased, remaining at 35 or 40 all afternoon and falling to 25 at 11:50. Next morning, the temperature was 101 F. and the respiratory rate was 180, but the dog was obviously sick, being scarcely able to move. At 11 a. m. he was dead. Autopsy showed edema of the neck near the site of injection. The trachea was clear. The chest was half filled with bloody fluid. The pericardium was adherent to the sternum. The interior of the pericardial sac was smooth. The heart was greatly dilated on the right side. There were emphysema and congestion of the lungs.

TABLE 5.—*Fatal Pneumonia*

Experiment 5				Experiment 7			
		Chlorine				Chlorine	
Date	Nitrogen Gm.	Gross Gm.	Net* Gm.	Date	Nitrogen Gm.	Gross Gm.	Net* Gm.
				3/31.....	7.14	1.02	....
2/ 9.....	3.46	0.425	.....	4/ 1.....	5.08	0.84	....
2/10.....	6.02	0.836	.....	4/ 2.....	8.81	1.38	....
2/11.....	3.90	0.419	0.371	4/ 3.....	5.06	2.26	2.16
2/12.....	6.96	0.181	0.157				
2/13.....	4.12	0.205	.....				
2/14.....	4.29	0.168	.....				
2/15.....	4.44	0.079	.....				
2/16.....	2.37	0.033	.....				
2/17.....	7.54	0.057	.....				

* This calculation was obtained by deducting the chlorine content of the broth injected into the animal.

Microscopic examination by Dr. Fraser showed extreme congestion and several areas of consolidation. His diagnosis was "acute bilateral hemorrhagic bronchopneumonia and pleuritis." The liver and kidneys showed granular degeneration.

COMMENT

As can be seen from an inspection of table 3, in each of the control experiments there was a marked drop in the excretion of chlorine. This fell to one fourth or one fifth of the previous amount. Correction for the amount of chlorine in the injected broth brings the amount excreted on the first day of the experiment down to one sixth or one fifth of that in the foreperiod. Subsequently, the amount of chloride in the urine increased, so that on the fourth day of fasting, it was two-fifths or one-half as great as in the foreperiod.

These results are in marked contrast to those obtained in the experiments in which pneumococcus cultures were injected into the same dog. The excretion of chloride was not reduced on the first day:

it remained unchanged, or was slightly increased, in the two experiments (62 and 63) in which only a slight pyrexia was induced, and was more than doubled in experiment 61, in which the effect on the dog's temperature and respiratory rate was more marked. On the second and third days, there was a corresponding diminution below the level observed in the control experiments. In experiments 62 and 63, it again rose to values resembling those obtained after the injection of sterile broth. In experiment 61, in which the initial loss of chlorine was the greatest, the depletion of the body's store of chlorine was great and the amount excreted remained low. However, here also, analyses of the individual voidings of urine disclosed, after the initial sharp rise and fall, a secondary rise in the ratio of chlorine to nitrogen

TABLE 6.—*Nitrogen and Chlorine Content of the Urine Obtained in Experiment 61*

Date	Nitrogen, Gm.	Chlorine, Gm.	100 Chlorine / Nitrogen
February 11	2.44*	2.060	84.5
	2.48	0.504	20.3
	1.48	0.079	5.3
February 12	0.81	0.088	10.8
	1.03	0.117	11.3
	1.01	0.041	4.1
	1.78	0.046	2.6
February 13	3.00	0.045	1.5
	1.89	0.017	0.9
	2.11	0.009	0.43
February 14	6.11	0.029	0.47

* Voided at about 6 p. m., eight hours after the first injection and five or six hours after the temperature began to rise.

(table 6). Later, this again diminished, just as it does in the fasting person.[27]

The experiment on dog 5 was unsatisfactory because some urine was retained from the first to the second day. Nevertheless, it is quite obvious, from a comparison of tables 4 and 5, that on the first day the excretion of chlorine was greater, and, on the second and third days, less than in the control experiments.

Dog 7, which succumbed to a severe pneumonitis (and septicemia?), showed a loss of chlorine that in proportion to the body weight, was even greater than that observed in experiment 61. Not less than 2 Gm. of "excess" chlorine was excreted in twenty-four hours. This is the equivalent of 0.26 Gm. of sodium chloride per kilogram of body weight, or of 16 Gm. of sodium chloride for a person weighing 62 Kg. (136 pounds).

Unfortunately, analyses of the blood or serum were not made, but it is scarcely conceivable that all of the chloride lost should have

been in the blood, for this could have contained only 3 Gm. of chlorine at the beginning of the experiment. The loss, per kilogram of body weight, was 0.16 Gm., or 4.51 milliequivalents. Assuming that the body fluids represent approximately two thirds of the body weight, and that the loss of chloride was evenly distributed, there was a diminution of 6 mg. per liter. This is not so great as that frequently observed in the plasma of patients with pneumonia, but is, nevertheless, considerable.

The significance of these results would appear to be obvious. If I had been unable to collect the urine during the first few hours of experimental pneumonia in dogs, as is the case in pneumonia in man, I might well have concluded that dogs with pneumonia excrete a smaller amount of chlorine than do normal, fasting dogs and that this relative retention continues for a day or two after the crisis of the disease.

At this point, reference must be made to the work of Medigreceanu,[30] who, in 1911, reported the results of two experiments on the metabolism of dogs infected with pneumococci by the method of Lamar and Meltzer.[28] Medigreceanu concluded that "The chlorine output is very much diminished during the process of experimental pneumonia in dogs (Tables I and II). The quantity of chlorine retained in the cases with well-developed exudates (Table I) is much larger than the exudate could account for."

The interpretation of Medigreceanu's tables is not quite simple. His table I is not at all clear. It is stated that the dog took no food on the two days following insufflation. Nothing is said of the day of insufflation. If food were taken on that day, the results obtained are incomprehensible, but if it were refused, the results are more nearly in agreement with those I obtained in experiments 62 and 63. Just as in these, the excretion of chlorine remained unchanged. Medigreceanu had no control experiments, and consequently failed to obtain results such as those shown in table 3. On the five days following insufflation, the excretion of chlorine was greatly reduced, but there was no subsequent increase above the normal during the remaining three days of the experiment. The three days before insufflation showed an average daily loss of 0.025 Gm. of chlorine. The following nine showed a net retention of 3.2 Gm., in spite of a loss of body weight of 0.5 Kg. and of 22 Gm. of nitrogen. What became of the retained chlorine is not clear. (If a ration had been taken on the day of insufflation, the amount of chloride to disappear would have been 5.6 Gm.)

30. Medigreceanu, F.: J. Exper. Med. **14**:289, 1911.

Medigreceanu's second dog had a less marked retention. The temperature did not rise quite so high, and there was no dulness or bronchial breathing. Apparently, the dog was not very ill, for the full ration was taken daily. During the control period, the ratio, 100 chloride : nitrogen, was 24 : 6. On the day of insufflation, it rose to 31 : 6. On the four following days, it was 9 : 2, 26 : 7, 28 : 2 and 24 : 6, respectively. These results seem to indicate an excess excretion of 0.58 Gm. of chlorine on the day of insufflation, followed by a retention of 1.13 Gm., accompanied by an increase in body weight, and then a loss of 0.19 and 0.14 Gm., respectively, on the two following days, as the body weight fell. The net change was an increased loss of 0.22 Gm.

Medigreceanu's experiments, therefore, cannot be accepted as contradicting the results here reported. On the contrary, the results of his second experiment are in harmony with the views expressed here.

The retention of chlorine is not peculiar to pneumonia. It has been observed in other fevers.[31] Curiously enough, malaria is an exception in that the febrile period is characterized by an increased excretion of chlorine. But malaria is precisely the condition in which it is possible to study changes during the onset of the fever. The loss of chlorine in a short period may be considerable, as much as 8 or 10 Gm. in six hours (Traube and Jochman[32] and von Limbeck[33]). Moreover, according to Ringer,[34] Terray[6] and von Moraczewski,[8] the greater part of the increased excretion occurs during the development of the fever and not during its height. The chlorine content of the plasma is reduced during the febrile period, while the rate of excretion is still greater than normal, indicating a lowered threshold for chloride.[35]

It is interesting to observe that McLean,[36] in 1915, concluded:

> Chloride retention in pneumonia is associated with a lowered concentration of chloride in the plasma, and failure of excretion is apparently due to this cause. The threshold is often considerably lowered during fever and usually returns to normal after the temperature becomes normal.

The full significance of these observations seems not to have been realized.

No observations on the retention of chlorine during the first few hours of pneumonia in man are available. Most of the records begin

31. Garratt, C. G.: Tr. Med.-Chir. Soc., London **87**:163, 1904.

32. Traube, L., and Jochman, P.: Deutsche Klin. **7**:511, 1855.

33. Von Limbeck, R.: Wien. med. Wchnschr. **44**:2129, 2182 and 2225, 1894.

34. Ringer, S.: Tr. Med.-Chir. Soc., London **43**:361, 1859.

35. Von Koranyi, A.: Ztschr. f. klin. Med. **34**:1, 1898. Liu, S. H.: Chinese J. Physiol. **2**:151, 1928.

36. McLean, F.: J. Exper. Med. **22**:36, 1915.

with the third day, or later. But, in 1880, Röhmann [5] reported a loss of 2.72 Gm. of chlorine on the third day and of 0.101 Gm. on the fourth day in a patient who retained 8 Gm., or more, of chlorine during the following six days. Von Moraczewski [8] observed a loss of 0.025 Gm. of chlorine on the fifth day (the first day of observation) in a patient who retained about 1 Gm. each day for the following six days and 0.52 and 0.38 Gm. on the seventh and eighth days, respectively. It is true that von Noorden [37] stated that, in one of his patients, he found only 2.2 Gm. of sodium chloride in the urine passed from the seventh to the thirty-first hours of the disease. This is a small amount for urine retained for twenty-four hours, but it may, nevertheless, represent a loss and not a retention. Moreover, from the results obtained in experiment 61 (table 6) and from the observations on malaria that have already been discussed, it is apparent that the initial discharge of chloride may well have been nearly, if not quite, completed by the end of the seventh hour after the patient recognized that he was ill.

However, the initial loss of chloride cannot account for all of the retention that is sometimes observed; neither does it explain the negative chlorine balances that are so frequently observed after the crisis of the disease. But, as I pointed out in the first part of this paper, it is possible that 5 or 6, or even 7 Gm., of sodium chloride should be held in the consolidated lung and that a considerably larger amount should accompany the water that is so frequently retained. The total of all three—initial loss, accumulation in the lung and solution in retained water—seems more than enough to account for the maximum retention of chloride that has, thus far, been observed.

The greatest positive balance of chloride reported in the literature seems to be that reported by Sunderman for his patient B_7. In six days, this patient retained $1{,}469 \pm 104$ milliequivalents of chlorine, or 86 ± 6 Gm. of sodium chloride. How was this distributed? In the first place, the chloride content of the serum was increased from 5.26 to 6.32 Gm. per kilogram of body weight. Assuming an increase of the same magnitude in all the body fluids and estimating these at two thirds of the body weight—59 Kg. at the beginning of the observation—the result is 42.4 Gm. sodium chloride. During the six days of the observation, the patient lost 56 Gm. of nitrogen and incurred a caloric deficit estimated by Sunderman as 7,300 calories. I have estimated that this represents a loss of tissue of 2.75 Kg. Since the patient gained 5.56 Kg., there must have been $5.56 + 2.75 = 8.33$ Kg. of water

37. Von Noorden, C.: Lehrbuch der Pathologie des Stoffwechsels für Aerzte und Studiernde, Berlin, A. Hirschwald, 1893, vol. 13, p. 222.

retained. If this is multiplied by 6.32, the concentration of sodium chloride at the end of the observations, the result is 52.4 Gm. The total of the two is 94.8 Gm. On deduction of the sodium chloride in the 2.75 Gm. of catabolized tissue, or 3.4 Gm., the net total is 91.4 Gm. The observed retention was 86 ± 6 Gm.

The case just discussed was complicated by the appearance of edema and of an abnormally high concentration of chloride in the serum. The next highest retention of chloride reported by Sunderman is also one of the highest recorded in the literature, and only Sunderman's data are sufficient for a complete analysis.

In this case the concentration of chloride in the serum increased from 4.86 to 5.56 Gm. per kilogram. Calculating that an increase of the same order occurred in all the tissue fluids, and that these constitute two thirds of the body weight, the result is 23.8 Gm. of sodium chloride.

TABLE 7.—*Retention of Chloride in Pneumonia* *

Sunderman's patient B7			Weight 59 Kg.
Final concentration of NaCl in serum			6.32 Gm. per liter
Initial concentration of NaCl in serum			5.26 Gm. per liter
			1.06
Estimate 40 liters tissue fluid at 1.06 Gm. per liter			42.4 Gm.
N. loss, 56 Gm.			
Calorie loss, 7,300; estimate	2.75 Kg.		
Gain in weight	5.56		
H_2O retained	8.33 Kg. at 6.32 Gm. per Kg.		52.4
			94.8
Deduct NaCl in tissue lost 2.75 × 1.24			3.4
			91.4

* The observed retention was 86 ± 6 Gm. The patient gained 1,050 Gm. in the first four days. The chloride rose from 90 to 99 mg. or from 5.26 to 5.79 Gm.

The loss of 68 Gm. of nitrogen and 4,000 calories in eight days indicates a loss of tissue of about 2.5 Kg. The actual loss in weight was only 1.76 Kg., indicating a retention of 0.74 Kg. of water. This would contain 4.1 Gm. of sodium chloride. The sum is 27.9 Gm. On deduction of the amount of sodium chloride in the catabolized tissue, estimated at 3.1 Gm., the net retention accounted for is 24.8 Gm. The actually observed retention was 37.5 ± 7.1 Gm. The agreement does not seem very good, but when one considers the numerous sources of error and the way in which they may all accumulate in this calculation, the divergence is not surprising.

It is therefore obvious why all attempts to find the retained chloride in the tissue were failures. The chloride was not accumulated in excess, but was retained in an effort to make good the previous losses.

Probably, these losses cannot be demonstrated in pneumonia in man, but they can and have been demonstrated in experimental pneumonia in dogs and in malaria in man.

The mechanism by which this loss is produced is not evident, but a possible clue may be found in the work of Balcar, Sansum and Woodyatt.[38] In the discussion of their results they wrote:

> It is proposed that in the ordinary febrile diseases, such as typhoid, tuberculosis and others, the symptom fever is due to a deficit of "free" water resulting from an abnormal tendency on the part of the colloids of the body to bind the water. The poison of the disease leads to changes of the cell colloids and increases their hydration capacities, so that they take up more water.
>
> The effect of this on the "free" water of the body is thus the same as that of thirst or the introduction of salt or sugar into the body from without.

TABLE 8.—*Retention of Chloride in Pneumonia* *

Sunderman's patient Bs	Weight 50.6 Kg.	
Final concentration of NaCl in serum	5.56 Gm. per liter	
Initial concentration of NaCl in serum	4.86 Gm. per liter	
	0.70	
Estimate 34 liters tissue fluid at 0.7 Gm. per liter		23.8 Gm.
N. loss, 68 Gm. Estimate, 2.5 Kg. tissue		
Calorie loss, 4,000 Gm.		
Actual loss in weight, 1.76 Kg.		
∴ 0.74 Kg. tissue replaced by water × 5.56		4.1 Gm.
		27.9
Deduct NaCl in tissue lost, 2.5 × 1.24		3.1
Total NaCl accounted for		24.8

* The observed retention was 37.5 ± 7.14 Gm.

Without necessarily subscribing to the interpretation that the fever in pneumonia and malaria is due to the increased hydration of the colloids, but merely accepting the view that, in these conditions, the colloids of the plasma bind more water than they normally do, the initial outpouring of chloride is easily understood.[39] If there is this difference

38. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

39. It is quite possible that the increased hydration of the plasma after exposure to high temperatures (Lozinsky, E.: Am. J. Physiol. **67**:388, 1923-1924. Barbour, H. G.; Dawson, M. H., and Neuwirth, L.: Ibid. **74**:204, 1925) or in cocaine fever (Barbour, H. G.: J. Pharmacol. & Exper. Therap. **427**:291, 1926) and the anhydremia due to cold (Barbour, H. G., and Hamilton, W. F.: Am. J. Physiol. **73**:385, 1925) may be due to the same effect of temperature on the capacity of the plasma proteins to combine with water. The diuresis following exposure to cold may, therefore, be caused in part, by the increased concentration of "free" water in the plasma and not, as is generally believed, entirely by the peripheral vasoconstriction.

between "free" and "combined" water, the excretion of sodium chloride would depend on its concentration in the "free" water. Diminution in the amount of the latter would lead to the increased concentration of sodium chloride therein. This would lead to an increased excretion. Thereafter, analyses of plasma or serum would show a diminished concentration of chloride, although the concentration in the "free" water might be normal, or even greater than normal. Later, as defervescence occurs, the concentration of "free" water may increase, and the patient may suffer from a lack of chloride.

The clinical significance of these observations is not altogether clear. It may be that the increased binding of water and the loss of chloride are parts of a protective mechanism. However, the fact that the greatest losses were observed in the dogs that showed the severest reactions indicates that this is not the case but that the loss is due to the toxemia or to the pyrexia. If that is so, the administration of chloride might be indicated.

On the other hand, because of the diminished amount of "free" water, a patient with fever and a chloride content of 85 milliequivalents per liter of plasma might react toward the administration of salt as would a person free from fever with a concentration of chloride in the plasma of 100 milliequivalents per liter. The reaction of the latter would depend on the ability of the kidneys to excrete the added chloride. If this were impaired, edema and circulatory disturbances might result. In a patient with pneumonia, the consequences might be serious. Again, if it were true that a concentration of 85 milliequivalents per liter of plasma is desirable in fever, a sudden return to normal temperature might find the patient with too little chloride unless some were promptly administered. Only careful trial and observation can determine under what conditions patients with pneumonia (and other fevers) should receive salt, but, in my opinion, it seems that the administration of salt is called for if the chloride content of the plasma or serum is below 90 milliequivalents per liter (0.53 Gm. sodium chloride per 100 cc.), and if the salt can be given without the appearance of edema. In any event, as soon as the temperature falls, an attempt should be made to restore the normal chloride content of the body fluid.[40] It is possible that some cases of postcritical collapse may be due to the sudden flooding of the body with water set free from combination with colloids, producing a too low osmotic pressure in the tissues. This might be effectively controlled by the administration of sodium chloride.

40. R. L. Haden is the latest protagonist of the administration of salt to patients with pneumonia. A review of the literature will be found in one of his papers (Am. J. M. Sc. **174**:744, 1927).

SUMMARY

1. The literature on the excretion of chloride in pneumonia is briefly reviewed. This shows that the diminished excretion of chloride in the urine is not due to loss in the perspiration or in the feces and that the retention cannot be accounted for by a simultaneous retention of water, by deposition in the lungs or by an increased concentration in other tissues.

2. The symptoms following the intratracheal or intrapneumonic injection of pneumococcus cultures in dogs are described.

3. Shortly after such injection, the amount of chloride in the urine is greatly increased. This is followed by a subnormal excretion.

4. From a review of the literature it is shown that the same sequence is observed in malaria in man.

5. It is suggested that the low concentration of chloride in the plasma in pneumonia is due to a rapid excretion of chloride in the early stages of the disease. Data from the literature are shown to support this view, while none could be found to oppose it.

6. Calculation of the changes observed in the patients showing the greatest recorded retentions of chloride in pneumonia show that the retention can be satisfactorily accounted for in terms of the hypothesis here presented.

7. The clinical significance of the results is briefly discussed.

Dr. George B. Wallace extended the facilities of his laboratory to me, and my assistants, Mr. Irving Levy and Mr. Paul Brandwein, did most of the analytic work.

DISCUSSION

DR. T. S. WILDER, Philadelphia: I think that our results can be shown best by means of slides. The first slide illustrates the difference shown by two infants with lobar pneumonia, seen fairly early, the first on a high salt intake and the second on a low salt intake. In the one there was an almost immediate rapid gain in weight and then a prompt loss following the crisis. In the other there was a rigid loss in weight amounting to 3 pounds (1.4 Kg.), and then an increase in weight following the crisis, after the amount of salt in the diet had been increased. This illustrates the excretion of base and chloride in the urine, showing a fairly high excretion from the first, a rise with the crisis and a reduction almost to zero at one point. One patient became extremely dehydrated while the intake of salt was low, and the other patient became edematous.

This slide illustrates the chart of the second case showing for five days a negative balance. At one point the balance was quite low. Then, following the crisis and an increase in the intake of salt, the balance became markedly positive. I should say that the second patient, the one that became dehydrated, received a large amount of water, practically 2 liters a day, and apparently could not retain the water without the salt.

This slide illustrates a case in which the intake of salt was very high. The patient retained a large amount of salt for the first few days, and then, just before death, excreted a tremendous amount, which showed that the kidneys were quite competent. The patient excreted a large excess of salt and yet retained a great deal.

The water curves in this slide show roughly that in infants on a high intake of water, 46, 71, 32 and 30 cc., the curve rose rapidly from the start; in those on a low intake, the curves dropped; in the ones on a moderate intake of about 15 cc., the weight remained high.

The question I should like to bring up is mainly this: If water is bound by the tissues, why should these infants on a very high intake of water, but receiving no salt, become dehydrated and lose weight steadily from the start?

DR. J. HAROLD AUSTIN, Philadelphia: I doubt the validity of Dr. Greenwald's assumption that a given change of chloride concentration in the water of the serum will be associated with an equal change in the chloride concentration in the water of the whole body, since the normal chloride concentration in the water of tissue cells is only about one fifth of that in the water of serum.

Nothing in Dr. Greenwald's data alters our view that it is reasonable to test clinically the program of supplying to the patient with pneumonia during the febrile period a sufficient amount of sodium chloride to permit the retention of salt appropriate to the retention of water exhibited during this period, provided the administration of salt is not pushed to the point of inducing gain in weight or edema. Clinical observation by us and by others seems to suggest benefit from such a regimen.

Dr. Greenwald invokes as an explanation of the early exaggerated outpouring of chloride in his infected dogs the postulate of Balcar, Sansum and Woodyatt of increased binding of water by body colloids during the febrile state with diminution of what Woodyatt and his associates called "free water." Dr. Greenwald assumes that this transfer of water from Woodyatt's "free" to "bound" state would reduce its power of holding chloride in solution. This assumption deserves examination.

Sunderman demonstrated within 2 per cent, the error of his method, that all of the water of serum is as free to dissolve chloride as is pure water, and Hill found the same to be true within 2 per cent, which was the error of his method, for the water of mammalian muscle and erythrocytes. It follows, then, that whatever may be meant by a tendency of the body colloids to bind water, there is not a particle of evidence to indicate that the power of the water to dissolve chloride will thereby be altered. Until experimental evidence is at hand that in the febrile state water is bound in serum or tissues in such a way as to alter its capacity for dissolving an electrolyte, it is not, I believe, useful to postulate such a mechanism in accounting for changes in the chloride concentration in the body.

DR. GREENWALD: In reply to the observations of Dr. Austin and Dr. Wilder, it seems to me that both Dr. Sunderman and Dr. Wilder have neglected to take into consideration the fact that the tissues contain chloride, and that when these are metabolized chloride is available for excretion. If this chloride is not excreted, it is as truly retained as any chloride that is administered.

If Dr. Wilder will take his figures for the nitrogen loss and look up the composition of the tissue of the human body, he will find that the chloride lost by the children who did not receive sodium chloride in the food was exactly equal to the calculated chloride content of the tissue represented by the loss of nitrogen.

In Sunderman's calculations, the body weight as a whole, including such tissues as bone, was employed. There is something wrong with his calculations. On two successive days, one person excreted 17 and 20 Gm. of nitrogen, resulting in a loss of 13 and 16 Gm., respectively. The urine contained only 0.2 milliequivalent of chloride on one day and none on the other. The total chloride in the urine and feces for the two days was only 2.7 milliequivalents. A more effective retention cannot be imagined. Nevertheless, Sunderman's method of calculation made it impossible for him to determine whether there was or was not a retention.

Dr. Austin has correctly pointed out that the concentration of chloride in the body fluids is only about one fifth of that in the plasma. But I am considering differences in concentration, not absolute values. If the concentration of chloride in the plasma is diminished, there must be a corresponding change in the concentration of chloride, or of some other substance capable of exerting osmotic pressure, in the tissue fluids.

It seems to me that we must assume that the disturbance of chloride metabolism in pneumonia must be the same regardless of the amount of chloride administered. The effects observed must be explained on this basis.

As to the question of bound water, the existence of bound water is purely hypothetic, but it is an attractive hypothesis. After eighty years of searching for this "retained" chloride, the existence of this bound water should not be ruled out simply because its presence has not been demonstrated. Conditions in normal defibrinated blood and in normal serum may be quite different from those in circulating plasma in patients with pneumonia.

METABOLISM IN PNEUMONIA

III. THE EXCRETION OF ANIONS AND OF TOTAL BASE IN PNEUMONIA *

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The striking retention of chloride in pneumonia, which I discussed in the preceding paper,[1] long ago stimulated investigation concerning the metabolism of other inorganic constituents. Salkowski [2] found that the excretion of sodium was greatly diminished while that of potassium was increased. Von Moraczewski [3] analyzed the urine and feces of one of his patients for potassium and sodium, and found that the retention of chlorine was accompanied by the retention of a somewhat smaller amount of sodium. There was a continued loss of potassium, which was to have been expected in view of the great loss of nitrogen, which varied from 10 to 22 Gm. per day.

In the same patient and in others, von Moraczewski [4] observed a retention of calcium. This observation was confirmed by Peabody,[5] who considered it of considerable significance. He made no control experiment and overlooked the fact that his patient received more than 2 Gm. of calcium per day, and that normal persons, unless previously on a diet high in calcium, would also show a retention if fed diets containing so much calcium. The diets employed by von Moraczewski contained less calcium, and, in his experiments, negative balances were sometimes observed even when the diet contained as much as 1 Gm. of calcium per day.

Von Hösslin [6] studied the excretion of phosphorus in the urine, but he found the results to be extremely variable and came to no definite conclusion. Von Moraczewski's [4] experiments on balance had previously shown a loss of phosphorous roughly paralleling the loss of nitrogen.

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* Submitted for publication, Nov. 10, 1930.

* From the Littauer Pneumonia Research Fund, New York University.

1. Greenwald, I.: Metabolism in Pneumonia. II. The Mechanism of the Retention of Chloride in Pneumonia, Arch. Int. Med., this issue, p. 418.
2. Salkowski, E.: Virchows Arch. f. path. Anat. **53**:209, 1871.
3. von Moraczewski: Virchows Arch. f. path. Anat. **55**:11, 1899.
4. von Moraczewski: Footnote 3; Ztschr. f. klin. Med. **39**:44, 1900.
5. Peabody, F. W.: J. Exper. Med. **17**:71, 1913.
6. von Hösslin, H.: Deutsches Arch. f. klin. Med. **93**:404, 1908.

Austin and Sunderman [7] analyzed specimens of urine obtained by Sunderman in his studies on chloride metabolism. They suggested that

> The low chloride excretion in the precritical period of pneumonia is dependent in large measure on low chloride intake and perhaps in part upon the need for excretion of excessive amounts of sulphate, phosphate, and organic acid under the handicap of little fixed base available for excretion. It is possible, furthermore, that this demand for fixed base for excretion is a factor in the low base concentration in the serum in the precritical period of pneumonia. Correlated with this would be a tendency for lowering of the serum chloride. Furthermore, in the need for transporting the increased amounts of sulphate, organic acids, and phosphate from the tissues to the kidneys we have perhaps a reason, although not a mechanism, for the disproportionate lowering of the serum chloride.

It appears that the failure to consider the influence of the loss of body tissue led Austin and Sunderman into error.

Calculations from data given by Sunderman [8] and by Austin and Sunderman [7] show that the patients with pneumonia excreted the following excesses of anions over cations per gram of nitrogen lost: B_1, 4.8 milliequivalents; B_2, 3.55 and 3.66; B_4, 2.2, 3.7 and 8.3; B_5, 5.92; B_6, 11 and 17; B_7 (eight days), 6.9; B_8 and B_9 (normal), 5 and 2.8, respectively. A similar calculation from data given by Benedict for his subject L. between the twelfth and the eighteenth days of the fast, assuming that the total sulphur comprised inorganic sulphate and ethereal sulphates in such amounts as to be equivalent to 75 per cent of the total expressed as sulphuric acid, gives an indicated excess of anions over cations of 4.2 milliequivalents per gram of nitrogen. Evidently, most of the values for the patients with pneumonia are normal. The few exceptions are apparently connected with a high intake of sodium chloride and may, perhaps, indicate that the retention of base is of more significance than that of chloride. However, in the absence of control experiments, no definite conclusion can be drawn.

In view of the great variation in the excretion of chlorine observed in some of the experiments described in the preceding paper, it seemed desirable to analyze the specimens of urine for other inorganic constituents. The lack of time did not permit a complete analysis of all of the specimens obtained. Those obtained in experiments 7 and 61 and in one of the control experiments were selected.

METHOD

The method of analysis employed for inorganic and ethereal sulphate was that of Folin.[9] The following method was used to determine the total phosphate and total base. The urine was oxidized with sulphuric and nitric acids. The acid

7. Austin, J. H., and Sunderman, F. W.: J. Clin. Investigation **7**:333, 1929.
8. Sunderman, F. W.: J. Clin. Investigation **8**:313, 1929.
9. Folin, O.: J. Biol. Chem. **1**:131, 1905.

mixture was transferred to a platinum crucible and evaporated to dryness. The residue was dissolved in water, made slightly alkaline with ammonium hydroxide and then slightly acid with acetic acid. Ferric chloride was added until a red color was produced, and after the addition of a few drops of a 3 per cent solution of a phosphate-free hydrogen dioxide, the mixture was heated to boiling and filtered. After being washed with hot water, the precipitate was dissolved in dilute nitric acid, and the phosphorus was precipitated with molybdate solution. The precipitate was filtered on a Gooch crucible fitted with a piece of filter paper and washed with a solution containing 5 per cent ammonium nitrate and 1 per

TABLE 1.—*Excretion of Anions and Total Base After the Injection of Sterile Broth; Experiment 32*

Date		Nitrogen, Gm.	Chlorine, Milliequivalents	Phosphate, Milliequivalents*	Inorganic Sulphate, Milliequivalents	Etheral Sulphate, Milliequivalents†	Total Anions, Milliequivalents	Total Base, Milliequivalents	Excess Anions, Milliequivalents	Comment
March	30	15.69	55.6	32.9	39.3	1.9	129.7	24.0	105.7	
	31	9.84	34.7	11.5	17.7	0.9	64.8	24.9	39.9	
April	1	10.69	22.0	24.8	31.0	1.2	79.0	16.0	63.0	
	2	11.02	28.2	37.3	28.8	1.1	95.4	13.5	81.9	
	3	1.06	2.76	5.46	3.0	0.09	11.31	0.05	11.26	Voided six hours after injection
		1.35	3.89	4.75	3.65	0.16	12.45	0.31	12.14	Voided six hours later
		1.94	3.72	20.0	5.96	0.40	30.08	0.00	30.08	Voided during night
Total	3	4.35	10.37	30.21	12.61	0.65	53.84	0.36	53.34	Injected broth contained 2.57 milliequivalents chlorine, 0.66 milliequivalents phosphorus and 4.61 milliequivalents total base
April	4	1.82	11.3	10.5	5.12	0.27	27.19	2.7	24.49	Injected broth contained 1.18 milliequivalents chlorine, 0.27 milliequivalents phosphorus and 1.66 milliequivalents total base
	5	3.87	26.9	17.4	9.7	0.52	54.5	24.8	29.7	Injected broth contained 1.11 milliequivalents chlorine, 0.27 milliequivalents phosphorus and 1.66 milliequivalents total base
	6	5.10	14.2	26.0	14.3	0.12	54.6	10.6	40.0	

* Calculated as 1.8 milliequivalents per millimol.
† Calculated as 1 milliequivalent per millimol.

cent nitric acid and then with alcohol. It was then titrated with a 0.1 per cent nitric acid and alkali, formaldehyde being used to remove the ammonia.

The filtrate from the basic acetate precipitate was evaporated to dryness, first in glass and then in a silica dish. After removal of most of the ammonium salts by gentle heating, the residue was transferred to a platinum crucible, evaporated to dryness and ignited. The residue was dissolved in dilute hydrochloric acid, and the sulphate content was determined by precipitation with barium chloride and weighing on a Gooch crucible.

COMMENT

Table 1 shows a remarkable diminution in the excretion of total base on the first two days of the injection of sterile broth. The amount of

total base was not only less than was required to combine with the excreted chlorine, but it was actually less than the amount injected with the broth.

Following the injection of the cultures (tables 2 and 3), there was a slight excess of base over that required to combine with the chlorine

TABLE 2.—*Excretion of Anions and of Total Base After the Injection of Pneumococcus Culture; Experiment 61*

Date	Nitrogen, Gm.	Chlorine, Milliequivalents	Phosphate, Milliequivalents*	Inorganic Sulphate, Milliequivalents	Etheral Sulphate, Milliequivalents†	Total Anions, Milliequivalents	Total Base, Milliequivalents	Excess Anions, Milliequivalents	Comment
February 6	8.50	25.5	20.2	19.8	0.9	66.4	24.7	41.7	
7	10.53	20.1	39.0	33.7	1.8	94.7	30.6	64.1	
8	7.75	33.0	44.7	30.8	1.4	109.9	19.5	90.4	
9	9.64	29.1	30.2	23.6	1.0	83.9	13.6	70.3	
10	11.51	30.2	26.4	27.2	1.2	85.0	12.1	72.9	
11	2.44	58.1	0.4	7.8	0.3	66.6	50.1	16.5	Voided eight hours after first injection
	2.48	14.2	16.4	8.6	0.4	39.6	30.2	9.4	Voided during night
	1.48	2.2	13.9	3.3	0.2	19.6	4.7	14.9	Voided next morning
Total 11	6.40	74.5	30.7	19.7	0.9	125.8	85.0	40.8	Injected culture contained 2.85 milliequivalents of chlorine, 0.59 milliequivalents of phosphorus, and 4.11 milliequivalents of total base
February 12	0.810	2.48	0.88	1.51	0.14	5.01	3.77	1.24	Voided three hours after injection
	1.033	3.30	0.14	1.82	0.09	5.35	5.11	0.24	Voided four hours later
	1.016	1.16	0.20	2.84	0.07	4.27	3.81	0.46	Voided four hours later
	1.778	1.30	0.38	3.75	0.15	5.58	5.46	0.12	Voided during night
Total 12	4.637	8.24	1.60	9.92	0.45	20.21	18.15	2.06	Injected culture contained 0.85 milliequivalents of chlorine, 0.19 milliequivalents of phosphorus, and 1.29 milliequivalents of total base
February 13	3.00	1.28	5.30	6.50	0.22	13.50	2.23	11.27	
	1.89	0.48	2.19	3.77	0.13	6.58	0.78	5.80	
	2.11	0.24	5.19	6.25	0.21	11.89	2.47	9.42	
Total 13	7.00	2.00	12.88	16.52	0.56	31.97	5.48	26.48	
February 14	6.11	0.80	4.01	9.50	0.31	14.62	0.98	13.64	

* Calculated as 1.8 milliequivalents per millimol.
† Calculated as 1 milliequivalent per millimol.

in the urine. The excess of total anions over total cations after the injection of the cultures was not greatly different from that after the injection of sterile broth.

Analysis of the individual voidings, as summarized in tables 1 and 2, shows a striking difference between the excretion of phosphorus in the first few hours after the injection of sterile broth and that after the

injection of a pneumococcus culture. In the latter case, though the length of time represented was greater by one-third and the nitrogen content of the urine was more than twice as great, the excretion of phosphorus was less than one tenth of what it was in the former.

This result is identical with that found in malaria by von Moraczewski.[3] It is interesting to read his description of the sequence of the changes in the excretion of the various elements.

Wenn wir uns also nach dem Gesagten ein Schema des Fiebers entwerfen wollten, so hätte dieses folgende Gestalt: Die erste Erhöhung der Temperatur soll eine Vermehrung des Chlors (Natrium, Kalium, Calcium, Ammoniak lasse ich aws, um das Bild nicht zu complicieren), eine Verminderung des Stickstoffs (oder Vermehrung), eine Verminderung des Phosphors nach sich ziehen.—Die zweite periode, wenn das Fieber unverändert andauert, zigt ein allmähliches Sinken der Chlorausscheidung, ein Steigen des Stickstoffs (oder verbleiben auf der früheren Höhe) ein Sinken des Phosphors.—Die dritte Periode—immer bei gleicher Temperatur—zeigt ein Sinken des Chlors, ein Steigen des Phosphors und des Stickstoffs, unzwar ist jetzt das Chlor unter Norm gesunken, Phosphor und Stickstoff über Norm gestiegen—jetzt haben wir den Ausscheidungstypus, der als Fieberharn bekannt ist. Dieses Bild kann nun andauern, wenn die Temperatur unverändert bliebt. Fällt die Temperatur (vielleicht durch Verdünnung des Blutes), so tritt das vierte Stadium ein, das Chlor wird noch mehr resiniert, der Phosphor und der Stickstoff noch mehr augescheiden. Dauert das Fallen der Temperatur, so erreicht Chlor das Minimum, Phosphor und Stickstoff ihr Maximum, und es ändert sich das Bild allmählich. Es tritt das fünfte Stadium ein, die Chlorausscheidung steigt bis zur Norm, Phosphor und Stickstoff kommen zur normalen Menge zurück.

(If in accordance with this we wish to outline a scheme of the fever, it would be as follows: The first increase in temperature should be followed by an increase in chlorine (I disregard the sodium, potassium, calcium and ammonia in order not to complicate the picture), an increase (or decrease) in nitrogen and a decrease in phosphorus. If the fever continues unchanged, the second period shows a gradual reduction in the elimination of chlorine, a gradual rise in the nitrogen (or a persistence at the former level) and a decrease in phosphorus. The third period—the temperature remaining the same—shows a decrease in chlorine and an increase in phosphorus and nitrogen; to be sure, the chlorine has now fallen below the normal and the phosphorus and nitrogen have increased above the normal. The type of elimination is now known as fever urine. This picture can persist only if the temperature remains unchanged. If the temperature decreases (perhaps as a result of a dilution of the blood), the fourth stage sets in: still more chlorine is retained and still more phosphorus and nitrogen are eliminated. If the fall in the temperature continues, the chlorine reaches the minimum and the phosphorus and nitrogen the maximum, and the picture changes gradually. Then the fifth stage develops in which the elimination of chlorine increases to the normal amount and the phosphorus and nitrogen have fallen to the normal quantities.)

It is amazing that von Moraczewski did not seem to realize that this initial outpouring of chlorine, which he observed in malaria, may have been so largely responsible for the retention that he and others observed in pneumonia.

There can be little doubt that the initial disturbance in the metabolism of chloride and phosphate in malaria and pneumonia (and probably other fevers) is much the same. In malaria, these data are available for study; in pneumonia, they are not. A possible explanation for the initial loss of chloride is presented in the preceding paper,[1] but the mechanism by which the retention of phosphorus is brought about is still unknown.

SUMMARY

1. A review of the literature on the excretion of anions and cations in pneumonia leads to the following conclusions: (*a*) The increased excretion of potassium is due to the increased destruction of tissue. (*b*) The retention of sodium roughly parallels that of chlorine. (*c*) The retention of calcium reported by some observers was due to a diet high in calcium and was not related to the pneumonia. (*d*) There is no marked disturbance in the anion-cation balance after the pneumonia has developed.

2. The intratracheal injection of sterile broth was followed on the first day by a marked diminution in the excretion of chlorine and by an even greater decrease in the excretion of total base. The amount of the latter in the urine was less than in the injected broth.

3. During the first few hours after the injection of pneumococcus cultures, the excretion of phosphorus was much less than after the injection of sterile broth. The same diminished excretion of phosphorus during the development of the fever has previously been observed by others in malaria in man.

4. It is concluded that the initial disturbance in the metabolism of chloride and phosphorus in malaria and in pneumonia is the same.

TABLE 3.—*Excretion of Anions and Total Base After the Injection of Pneumococcus Culture; Experiment 7*

Date	Nitrogen, Gm.	Chlorine, Milliequivalents	Phosphate, Milliequivalents*	Inorganic Sulphate, Milliequivalents	Etheral Sulphate, Milliequivalents†	Total Anions, Milliequivalents	Total Base, Milliequivalents	Excess Anions, Milliequivalents	Comment
March 31	7.14	28.8	13.9	14.1	0.7	57.5	33.9	23.6	
April 1	5.08	23.7	6.1	10.3	0.4	40.5	27.2	13.3	
2	8.81	38.9	20.8	18.7	1.0	78.4	48.3	30.1	
3	5.06	63.8	29.9	12.7	0.8	107.2	65.0	42.2	Injected culture contained 2.9 milliequivalents of chlorine, 0.5 milliequivalents of phosphorus and 3.5 milliequivalents of total base

* Calculated as 1.8 milliequivalents per millimol.
† Calculated as 1 milliequivalent per millimol.

THE SIGNIFICANCE OF CEREBROSPINAL FLUID SUGAR *

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The purpose of this report is to add further data to that already recorded, in order to establish more definitely the relationship of the sugar in the blood and in the cerebrospinal fluid in health and disease. Although the cerebrospinal fluid has been the subject of chemical investigation for many years, it was not until an increase in the sugar in the spinal fluid was said to be diagnostic of epidemic encephalitis that quantitative determinations of sugar were given especial attention.

The amount of sugar in normal spinal fluid was at first determined by the examination of fluids promiscuously obtained. Some of these results, which were extremely variable, were undoubtedly influenced by the different methods of examination, while others were affected by the level of the blood sugar.

Shrewsbury and Williamson [1] examined 151 fluids by the Folin-Wu method. In an attempt to throw more light on the theory that glycolysis occurs rapidly, they made two readings of each of 16 fluids. Fluids examined within one hour after removal were from 1 to 8 mg. higher in sugar content than when they were examined twelve hours later.

Halliday [2] accounted for some of the high readings of sugar in the spinal fluid by the fact that the sugar curves in the cerebrospinal fluid correspond to the sugar curves in the blood, but are delayed. He found that the amount of sugar in the spinal fluid was from 50 to 70 per cent as high as the amount of sugar in the blood when the specimens were obtained at the same time after the patients had fasted for several hours. In twenty cases of encephalitis, the amount of sugar in the blood varied from 68 to 128 mg. and the amount of sugar in the spinal fluid from 42 to 70 mg.

In a comparative study of the sugar in the blood and in the spinal fluid in 206 cases of nervous and mental disease, Saye [3] found the

* Submitted for publication, Dec. 10, 1930.

1. Shrewsbury, J. F. D., and Williamson, G. F.: Critical Review of the Cerebrospinal Fluid Sugar, J. Neurol. & Psychopath. **9**:11 (July) 1928.

2. Halliday, J. L.: Spinal Fluid Sugar in Encephalitis, Quart. J. Med. **18**:300 (April) 1925.

3. Saye, E. B.: Dextrose Content of Cerebrospinal Fluid in Certain Nervous and Mental Diseases, J. M. A. Georgia **15**:92 (March) 1926.

amount of sugar in the spinal fluid the same in psychotic as in normal patients. He considered the normal quantity to be from 40 to 60 mg.

Fremont-Smith and Daily [4] pointed out that blood sugar curves are followed by similar curves in the spinal fluid; so at one stage, the content of sugar in the spinal fluid might be found high after the sugar in the blood had returned to a normal level. They found sugar in the spinal fluid above 80 mg. in many conditions other than encephalitis. These instances of high sugar content in the spinal fluid are usually associated with hyperglycemia, which may be due to a metabolic disorder or to cerebral lesions. In four cases, they found an increase of from 6 to 9 mg. of sugar in the spinal fluid after an interval of from one to one and one-half hours following oral or intravenous administration of dextrose.

Greenfield and Carmichael [5] considered the normal limits of sugar in the spinal fluid to be from 45 to 85 mg. In their experience, an increase in the sugar content of the spinal fluid is usually a reflection of an increase in the sugar content of the blood and is most likely to occur in diabetes mellitus or in nephritis, although the sugar in the spinal fluid may be slightly increased in any condition that increases the intracranial pressure. Except in these conditions, Greenfield and Carmichael do not believe that the amount of sugar in the spinal fluid ever exceeds 100 mg.

Goodwin and Sheeley [6] are of the opinion that the sugar in the spinal fluid does not maintain a constant level in the same person and that there is no level within reasonable limits that might be considered normal for different persons. In their experience, the amount of sugar in the spinal fluid is normally, fairly constant at from 45 to 65 per cent of the amount of sugar in the blood.

Grayzel and Orent,[7] experimenting on dogs, demonstrated the effect on the sugar in the spinal fluid of an increase in the sugar in the blood and proved the latent rise of the fluid sugar curve. Cistern punctures were made on dogs. Samples of blood and of spinal fluid were taken after the dogs had fasted and after the intraperitoneal administration of from 0.5 to 1.0 Gm. of dextrose per kilogram.

Specimens were again taken at intervals of fifteen, thirty and sixty minutes for from six to seven hours. The whole blood showed a sharp

4. Fremont-Smith, F., and Dailey, M. E.: Cerebrospinal Fluid Sugar, Arch. Neurol. & Psychiat. **14**:390 (Sept.) 1925.

5. Greenfield and Carmichael: The Cerebrospinal Fluid in Clinical Diagnosis, New York, The Macmillan Company, 1925.

6. Goodwin, G. M., and Shelley, H. J.: Sugar Content of Cerebrospinal Fluid and its Relation to the Blood Sugar, Arch. Int. Med. **35**:242 (Feb.) 1925.

7. Grayzel, H. G., and Orent, E. R.: Blood and Cerebrospinal Fluid Sugar, Am. J. Dis. Child. **34**:1007 (Dec.) 1927.

rise in twenty-seven minutes and the plasma in thirty-nine minutes, while the spinal fluid reached its maximum in two hours and thirty minutes. The return to the normal level was in proportion to the rise. The whole blood reached the normal level in three hours and twenty minutes, the plasma in four hours and twenty minutes and the spinal fluid in from six to seven hours. In the animals that had fasted for ten hours, these authors found that the amount of sugar in the normal spinal fluid varied from 40 to 75 mg.

In a series of syphilitic patients, Becker [8] found a tendency to low values of sugar in the cerebrospinal fluid when the cell count was high and the changes in the colloidal benzoin reactions occurred in the first zone. He attributed this tendency to low values to an alteration in the permeability of the meninges and of the choroid plexus by the infection. An alimentary hyperglycemia showing a blood sugar content of 185 mg. per hundred cubic centimeters had no effect on the sugar in the spinal fluid, nor did five months of intensive treatment affect it.

Wilcox, Lyttle and Hearn [9] advocated examination of the sugars in the blood and in the spinal fluid on specimens simultaneously obtained. Under such conditions, they found that the amount of sugar in the spinal fluid was from 40 to 60 per cent of the amount of sugar in the blood. Since high values occur in epidemic encephalitis, acidosis, meningitis, convulsions, nephritis and poliomyelitis of the bulbar type, this evidence cannot be considered diagnostic.

Additional evidence to support the theory that the spinal fluid is affected by the concentration of the sugar in the blood was recently furnished by Katzenelbogen.[10] Experimenting with rabbits, he was able to alter both the sugar in the blood and in the spinal fluid by injections of dextrose, insulin and epinephrine. However, the meningeal permeability to dextrose varies in different, apparently healthy rabbits. It may also vary in the same rabbit from day to day without any apparent change in condition.

Penfold and Irving [11] recently published results that correspond more closely to the observations in this series of cases than do those of other investigators (table 1). In their series, the average amount of cerebrospinal fluid sugar was 76 mg. and the lowest reading showed 68 mg.

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8. Becker, S. W.: The Sugar and Chloride Content of Cerebrospinal Fluid with Special Reference to Neurosyphilis, J. Lab. & Clin. Med. **12**:43 (Oct.) 1926.

9. Wilcox, H. B.; Lyttle, J. D., and Hearn, J. E.: Chemical Composition of Spinal Fluid: Diagnostic Value, Am. J. Dis. Child. **30**:513 (Oct.) 1925.

10. Katzenelbogen, S.: Experimental Study on the Sugar in Blood and Cerebrospinal Fluid, J. Pharmacol. & Exper. Therap. **36**:231 (June) 1929.

11. Penfold, W. J., and Irving, D. H.: Refractive Index of Cerebrospinal Fluid as Check on Chemical Analysis, M. J. Australia **1**:772 (June 14) 1930.

In each case reported in the accompanying tables, the blood and spinal fluid were drawn simultaneously after the patient had fasted for at least twelve hours. The readings were made within one hour after the specimens were obtained. Epstein's microchemical method on the principle of the Lewis-Benedict method was used in most instances. The

TABLE 1.—*Observations of Some Investigators*

Author	Normal Spinal Fluid Sugar	Summary
Alpers, B. J., Campbell, C. J., and Prentiss, A. M.: Arch. Neurol. & Psychiat. **11**: 653 (June) 1924	50-60 mg.	Average amount of spinal fluid sugar in cases of encephalitis, 82 mg.; in cases of dementia praecox, 83 mg.
Cookson: Brit. M. J. **1**: 157, 1925.....	.....	High content of spinal fluid sugar in all cases of encephalitis in series
Crawford and Cantarow: Am. J. M. Sc. **171**: 859, 1926	.....	High content of globulin and sugar in spinal fluid characteristic of increased intracranial pressure; high spinal fluid sugar content in mental disorders
Foster and Cockrell: Am. J. M. Sc. **167**: 696, 1924	.....	Sugar content over 60 mg. in 34 of 35 cases of encephalitis
Kuhle and Schultz: J. Exper. Med. **42**: 565, 1925	33-81 mg.	33-81 per cent of blood sugar
Levinson, A.: Am. J. Dis. Child. **30**: 774 (Dec.) 1925. Cerebrospinal Fluid in Health and in Disease, ed. 2, St. Louis, C. V. Mosby Co., 1923	64-106 mg.	
Nixon, C. E., and Egerer-Seham, G.: Arch. Int. Med. **28**: 561 (Nov.) 1921	45-95% of blood sugar	
Purves-Stewart, James: Diagnosis of Nervous Diseases, New York, E. B. Treat & Company, 1924	.....	High content of spinal fluid sugar in encephalitis in contrast with low values in tuberculous meningitis and early poliomyelitis
Reger, J. B.: Boston M. & S. J. **175**: 817, 1916	.....	From 134 to 256 mg. of spinal fluid sugar in cases of diabetes mellitus
Schloss, A. M.: Am. J. Dis. Child. **11**: 1 (Jan.) 1916	53-130 mg.	
Spurling, R. G., and Maddock, C. L.: Arch. Neurol. & Psychiat. **14**: 54 (July) 1925	57-84 mg.	
Stowe, W. P.: J. Lab. & Clin. Med. **11**: 307, 1926	60-91 mg.	"High" in two cases of encephalitis; from 10 to 15 mg. in tuberculous meningitis
Thalheimer, W., and Updegraff, H.: Arch. Neurol. & Psychiat. **8**: 15 (July) 1922; J. A. M. A. **78**: 1383 (May 6) 1922	Upper limits 60-65 mg.	
Wittgenstein, A.: Deutsche med. Wchnschr. **49**: 246, 1923	45-60 mg.	

readings from the Folin-Wu method did not vary materially from the microchemical readings. Readings were checked at short intervals by the Lewis-Benedict method so that fading of the standard would not affect the results.

Although a manometer was used to determine the pressure of the fluid in many of the recorded cases, the results are tabulated in the tables in other terms. In many cases, punctures were made while

TABLE 2.—*Encephalitis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	42	Clear	N.†	3	Neg.	84	100	84	Neg.	Neg.	Chronic encephalitis
W	M	18	Clear	N.	2	Neg.	90	105	85	Neg.	Neg.	Chronic encephalitis
W	M	3	Clear	+4	3	Trace	80	110	72	Neg.	Neg.	Encephalitis following whooping cough
C	F	11	Cloudy	+2	1380	+2	80	118	67	Neg.	Neg.	Clinically typical acute encephalitis
			Slightly cloudy	N.	450	Neg.	80	120	66	Neg.	Neg.	
			Clear	N.	16	Neg.	100	128	78	Neg.	Neg.	Greatly improved
			Clear	N.	2	Neg.	84	102	82	Neg.	Neg.	
			Clear	N.	3	Neg.	86	112	76	Neg.	Neg.	Improving
			Clear	N.	16	Neg.	94	118	79	Neg.	Neg.	
			Clear	N.	6	Neg.	80	102	78	Neg.	Neg.	
			Clear	N.	2	Neg.	75	100	75	Neg.	Neg.	
			Cloudy	Slight increase	440	Trace	60	110	54	Neg.	Neg.	Acute exacerbation
			Cloudy	+1	440	Trace	80	130	61	Neg.	Neg.	Neutrophils 90 per cent
			Cloudy	+1	188	Trace	80	120	66	Neg.	Neg.	Irregular fever; stuporous
			Cloudy	N.	150	Trace	90	130	69	Neg.	Neg.	Neutrophils 50 per cent
			Cloudy	N.	88	Trace	84	112	75	Neg.	Neg.	Cells all lymphocytes
			Clear	N.	35	Neg.	90	126	70	Neg.	Neg.	
			Cloudy	N.	11	Trace	80	98	81	Neg.	Neg.	Improving
			Clear	N.	8	Neg.	90	110	81	Neg.	Neg.	
			Clear	N.	10	Neg.	103	150	68	Neg.	Neg.	Improving
			Clear	N.	2	Neg.	92	116	79	Neg.	Neg.	Removed from hospital by parents
W	M	13	Clear	+4	120	Trace	80	95	84	Neg.	Neg.	Acute encephalitis
			Clear	+2	15	Neg.	90	100	90	Neg.	Neg.	Complete recovery in eight days
C	M	27	Clear	N.	5	Neg.	115	125	90	Neg.	Neg.	Postencephalitis; Parkinson's syndrome
W	M	9	Clear	+4	74	+3	95	110	86	Neg.	Neg.	Acute encephalitis with bulbar paralysis
			Clear	+2	50	Trace	94	105	89	Neg.	Neg.	Bulbar symptoms disappearing
			Clear	N.	28	Trace	103	101	101	Neg.	Neg.	Marked improvement
			Clear	N.	14	Neg.	100	110	90	Neg.	Neg.	Clinically well
			Clear	N.	13	Neg.	80	105	76	Neg.	Neg.	Apparently well twelve days after onset

TABLE 2.—*Encephalitis—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	5	Cloudy	+3	100	+2	118	130	78	Neg.	Neg.	Acute encephalitis
W	F	27	Clear	N.	8	Neg.	75	100	75	Neg.	Neg.	Chronic encephalitis
W	M	44	Clear	N.	7	Neg.	78	118	66	Neg.	Neg.	Chronic encephalitis
W	M	49	Clear	N.	4	Neg.	80	120	66	Neg.	Neg.	Chronic encephalitis
W	M	26	Clear	N.	3	Neg.	78	112	69	Neg.	Neg.	Postencephalitic neurasthenia
W	M	26	Clear	N.	1	Neg.	90	118	76	Neg.	Neg.	Chronic encephalitis
W	M	20	Clear	N.	3	Neg.	90	120	75	Neg.	Neg.	Chronic encephalitis
W	F	32	Clear	+3	68	+1	85	100	85	Neg.	Neg.	Acute encephalitis
W	F	11	Clear	+4	120	+2	90	115	78	Neg.	Neg.	Acute encephalitis
W	M	9	Clear	+3	90	+2	85	95	89	Neg.	Neg.	Acute encephalitis
W	M	30	Clear	+2	110	+1	90	110	82	Neg.	Neg.	Acute encephalitis
W	M	22	Clear	+2	60	+1	86	108	79	Neg.	Neg.	Acute encephalitis
C	F	13	Cloudy	+3	220	+3	75	90	83	Neg.	Neg.	Acute encephalitis
Average (20 cases).....							87	112	77			

* Ratio of spinal fluid sugar to blood sugar.

† In this and the following tables N. indicates normal.

the patients were being forcibly held and it was, therefore, impossible to get them in the relaxed horizontal position that is desirable when a manometer is used. The pressure was considered normal when the fluid flowed in successive drops at a rate of more than twenty drops per minute when the stilet was first removed. When the fluid spurted in a stream from the needle, the pressure was recorded as + 4. An 18 gage needle was used on adults and a 22 gage needle on infants and small children. Although this method of determining the pressure of the spinal fluid is somewhat gross, the results are satisfactory for clinical purposes.

SUMMARY

Two hundred and one readings were made on both the blood and the spinal fluid of 145 patients.

Forty-two readings in twenty cases of encephalitis gave an average of 87 mg. for the sugar in the spinal fluid and 112 mg. for the sugar in the blood with a ratio of 77 per cent (table 2). It is interesting to note that thirty-two readings on ten patients with acute encephalitis

gave exactly the same averages as did the readings on the entire group of patients with encephalitis. In one instance, the amount of sugar in the spinal fluid was higher than the amount of sugar in the blood. This occurred in a white boy, aged 9, when the acute symptoms were beginning to subside.

TABLE 3.—*Syphilis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
C	F	25	Clear	N.	2	Neg.	80	108	74	Neg.	Neg.	Syphilitic cirrhosis
W	M	6 0	Clear	N.	1	Neg.	90	100	90	Neg.	Neg.	Old tabes
C	M	51	Clear	N.	10	Trace	82	105	78	Neg.	Neg.	Clinical neurosyphilis,; Wassermann reaction of the blood positive; rapid improvement under treatment
W	M	62	Clear	N.	3	Trace	68	80	85	+4	Neg.	Neurosyphilis
W	M	40	Clear	N.	11	Trace	75	100	75	+4	Neg.	Tabes
W	M	59	Clear	N.	9	Neg.	70	106	66	+3	Neg.	Tabes
W	M	51	Clear	N.	40	+2	78	110	70	+4	Neg.	Paresis
W	M	45	Clear	N.	11	Trace	80	120	66	+	Neg.	Paresis; treatment given for one year
W	F	38	Clear	N.	13	Trace	76	110	69	+4	Neg.	Tabes
W	F	50	Clear	N.	27	+2	70	90	77	+4	Neg.	Taboparesis
W	M	38	Clear	N.	68	+3	90	124	72	+4	Neg.	Neurosyphilis
W	F	14	Clear	N.	3	Neg.	80	122	65	Neg.	Neg.	Congenital syphilis
W	M	60	Clear	N.	6	Neg.	88	100	88	Neg.	Neg.	Periostitis of the frontal bone; clinically diagnosed as neurosyphilis
W	M	42	Clear	N.	32	+2	70	113	69	+4	Neg.	Neurosyphilis
Average (14 cases)							79	106	74			

* Ratio of spinal fluid sugar to blood sugar.

Fourteen patients with syphilis showed an average of 79 mg. of sugar in the spinal fluid and of 106 mg. of sugar in the blood, with a ratio of 74 per cent (table 3).

Thirty-three patients with miscellaneous neurologic lesions showed an average of 84 mg. of sugar in the spinal fluid and an average of

TABLE 4.—*Miscellaneous Neurologic Cases*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio,* per Cent	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	28	Clear	N.	10	Trace	90	110	81	Neg.	Neg.	Acute myelitis; cord emulsion failed to give positive results after inoculation of rabbits and guineapigs
W	M	26	Clear	N.	3	Neg.	78	114	68	Neg.	Neg.	Healed myelitis with spastic paraplegia
W	M	41	Clear	N.	14	Trace	90	120	75	Neg.	Neg.	Myelitis following exhaustion from heat
W	M	19	Clear	N.	2	Neg.	80	105	76	Neg.	Neg.	Acute malaria with symptoms of cerebral thrombosis
C	F	14	Clear	N.	4	+1	100	110	90	Neg.	Neg.	Paramyoclonus multiplex
C	F	18	Clear	N.	5	Neg.	82	102	80	Neg.	Neg.	Bilateral cervical ribs; spastic quadraplegia
W	F	13	Clear	+3	10	+1	95	115	82	Neg.	Neg.	Acute uremia
W	F	15	Clear	N.	1	Neg.	85	110	77	Neg.	Neg.	Unclassified type of familial disease of central nervous system
W	M	56	Clear	N.	2	Neg.	80	104	77	Neg.	Neg.	Cerebral thrombosis
C	M	60	Clear	N.	192	+1	90	120	75	Neg.	Neg.	Tic douloureux, occurring two days after injection of alcohol; neutrophils, 50 per cent
C	M	24	Clear	N.	2	Neg.	108	120	90	Neg.	Neg.	Cerebral thrombosis
C	M	40	Clear	N.	2	Trace	80	110	72	Neg.	Neg.	Syringomyelia
W	M	22	Clear	N.	2	Neg.	80	104	77	Neg.	Neg.	Pseudobulbar paralysis
C	M	10	Clear	N.	1	Neg.	90	105	85	Neg.	Neg.	Narcolepsy
W	M	24	Slightly yelow	Decreased	8	Trace	84	102	82	Neg.	Pos.	Pachymeningitis
			Clear	Decreased	76	Trace	90	110	81	Neg.	Pos.	Recovery in six months
W	M	30	Clear	N.	2	Neg.	100	130	76	Neg.	Neg.	Paralysis agitans
W	M	30	Clear	N.	4	Trace	92	112	82	Neg.	Neg.	Amyotrophic lateral sclerosis
W	M	49	Clear	N.	10	Neg.	80	115	69	Neg.	Neg.	Cerebral arteriosclerosis; hypertrophic arthritis

* Ratio of spinal fluid sugar to blood sugar.

TABLE 4.—*Miscellaneous Neurologic Cases—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	56	Clear	N.	5	Neg.	88	112	78	Neg.	Neg.	Old fracture of first lumbar vertebra; cord injury
C	M	42	Clear	N.	1	Neg.	80	140	63	Neg.	Neg.	Pulmonary tuberculosis; parkinsonian tremor of unknown etiology
C	M	19	Clear	N.	8	Neg.	75	104	72	Neg.	Neg.	Bell's paralysis
W	M	42	Clear	N.	3	Neg.	85	108	78	Neg.	Neg.	Vertigo; cause unknown
W	M	70	Clear	N.	1	Neg.	86	110	78	Neg.	Neg.	Cerebral arteriosclerosis
W	M	57	Yellow	Low	13	Trace	74	110	67	Neg.	Pos.	Tumor of the spinal cord
W	F	30	Clear	N.	4	Neg.	72	108	66	Neg.	Neg.	Old poliomyelitis
W	M	40	Clear	−1	11	Trace	74	118	62	Neg.	Neg.	Chronic alcoholism; Korsakoff's syndrome
W	M	38	Clear	N.	7	Neg.	76	100	76	Neg.	Neg.	Pulmonary tuberculosis; cerebellar tubercle
W	M	48	Clear	N.	2	Neg.	72	112	64	Neg.	Neg.	Progressive muscular atrophy
W	M	27	Clear	N.	3	Neg.	85	110	77	Neg.	Pos.	Pott's disease; obstruction to iodized poppy seed oil 40% from 6th to 8th dorsal vertebra
W	M	73	Clear	N.	2	Neg.	90	112	80	Neg.	Neg.	Cerebral arteriosclerosis
W	F	59	Clear	N.	47	Trace	75	105	71	Neg.	Neg.	Cerebral softening
			Clear	Low	40	Trace	90	110	81	Neg.	Pos.	
W	F	65	Clear	N.	3	Neg.	72	110	65	Neg.	Neg.	Hemiplegia
C	F	10	Clear	N.	1	Neg.	78	105	74	Neg.	Neg.	Peripheral neuritis
Average (33 cases).....							84	111	75			

* Ratio of spinal fluid sugar to blood sugar.

111 mg. of sugar in the blood, with a ratio of 75 per cent. The highest reading for sugar in the spinal fluid in this group was 100 mg. and occurred in a patient with paramyoclonus multiplex. This represented a ratio of 90 per cent (table 4).

TABLE 5.—*Meningitis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Quickenstedt Reaction	Comment
W	M	5	Cloudy	+4	2,460	+2	70	94	74	Neg.	Neg.	Streptococcus meningitis, spinal fluid sugar quickly dropped to zero; death in 25 days
C	F	30	Cloudy	+3	760	+2	30	106	28	Neg.	Neg.	Tuberculous meningitis
W	M	11	Clear	+2	388	+1	55	90	61	Neg.	Neg.	Tuberculous meningitis
			Cloudy	+3	1,042	+2	84	110	30	Neg.	Neg.	
			Cloudy	+1	983	+1	22	100	22	Neg.	Neg.	
			Cloudy	+1	1,486	+1	0	108	0	Neg.	Neg.	Death occurred
W	F	8	Cloudy	+4	1,124	+2	64	110	58	Neg.	Neg.	Streptococcus meningitis
			Cloudy	+2	743	+2	30	100	30	Neg.	Neg.	
			Cloudy	+2	974	+2	0	90	0	Neg.	Neg.	Died
W	M	18 mo.	Cloudy	+3	2,400	+2	0	120	0	Neg.	Neg.	Tuberculous meningitis; neutrophils, 65 per cent
			Cloudy	+3	1,100	Trace	40	120	33	Neg.	Neg.	Neutrophils, 40 per cent
C	F	30	Cloudy	+2	1,360	+2	30	100	30	Neg.	Neg.	Tuberculous meningitis
W	F	25	Yellow and cloudy	+4	1,611	+2	116	144	80	Neg.	Pos. on affected side	Streptococcus septicemia and meningitis; thrombosis of the left cavernous sinus
W	M	17	Clear	+2	250	Trace	82	100	82	Neg.	Neg.	Bilateral otitis media; mastoiditis; lobar pneumonia; pleurisy with effusion; acute nephritis; meningitis (?); no organisms recovered from fluid
			Clear	Decreased	62	Trace	90	120	75	Neg.	Neg.	
			Clear	Decreased	20	Neg.	84	106	79	Neg.	Pos.	
			Slightly cloudy	Decreased	22	Trace	84	110	76	Neg.	Pos.	
			Clear	Decreased	12	Trace	90	110	81	Neg.	Neg.	Mentally clear
			Clear	N.	10	Neg.	82	105	78	Neg.	Neg.	
			Clear	N.	3	Neg.	96	125	76	Neg.	Neg.	Complete recovery after two months
W	F	36	Cloudy	+1	844	+3	10	90	11	Neg.	Neg.	Tuberculous meningitis
W	M	22	Cloudy	+2	560	+2	0	110	0	Neg.	Neg.	Tuberculous meningitis

* Ratio of spinal fluid sugar to blood sugar.

TABLE 5.—*Meningitis—Continued*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Quickenstedt Reaction	Comment
W	M	42	Clear	+1	68	Trace	68	112	60	Neg.	Neg.	Tuberculous meningitis
			Clear	N.	50	Trace	66	100	66	Neg.	Neg.	Pott's disease
			Slightly cloudy	+1	74	Trace	60	114	52	Neg.	Neg.	
			Cloudy	+2	68	+1	52	110	47	Neg.	Neg.	
			Cloudy	+1	114	+1	42	90	46	Neg.	Neg.	
			Cloudy	+1	108	+1	45	108	41	Neg.	Neg.	
			Cloudy	Slight increase	278	+1	30	100	30	Neg.	Neg.	
			Cloudy	+1	580	+1	25	114	22	Neg.	Neg.	
			Cloudy	+1	464	+2	22	106	20	Neg.	Neg.	
			Cloudy	+1	320	+1	15	100	15	Neg.	Neg.	
			Cloudy	+1	420	+2	0	94	0	Neg.	Neg.	
			Cloudy	+1	540	+2	0	90	0	Neg.	Neg.	Died
C	F	30	Cloudy	+4	430	+2	30	114	26	Neg.	Neg.	Tuberculous meningitis
			Cloudy	+2	380	+1	15	100	15	Neg.	Neg.	
			Cloudy	+2	244	+1	15	85	17	Neg.	Neg.	
			Cloudy	+2	412	+1	0	110	0	Neg.	Neg.	
			Cloudy	+2	390	+1	0	106	0	Neg.	Neg.	Died
Average (12 cases).....							36	105	34			

* Ratio of spinal fluid sugar to blood sugar.

Thirty-nine readings were made on twelve patients with meningitis (table 5). The average amount of sugar in the spinal fluid for the group as a whole was 36 mg. and the average amount of sugar in the blood was 105 mg., giving a ratio of 34 per cent. Of this group, eight patients had tuberculous meningitis, and the average quantity of sugar in the spinal fluid in these eight patients was 27 mg., which represented a ratio of 26 per cent. The remaining four cases are somewhat misleading, as some of them were not followed long enough to determine the effect of prolonged infection. The average amount of sugar in the spinal fluid in these four cases was 74 mg., which was 68 per cent of the average amount of sugar in the blood. The tendency of the sugar in the spinal fluid to decrease in tuberculous and purulent meningitis as shown in table 5 corresponds to the observations of other investigators.

The observations in multiple sclerosis and combined sclerosis are of no diagnostic significance (table 6 and 7).

Five patients with diabetes mellitus showed the effect of a high content of sugar in the blood on the sugar in the spinal fluid. However,

the relationship of the sugar in the blood and the sugar in the spinal fluid remains within normal limits (table 8).

The sugar in the spinal fluid of ten patients with nervous and mental disorders showed a slightly higher average than in many of the groups (table 9), being 88 mg. and representing a ratio of 79 per cent.

TABLE 6.—*Multiple Sclerosis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Quickenstedt Reaction	Comment
W	M	39	Clear	N.	9	Neg.	80	120	66	Neg.	Neg.	
W	F	24	Clear	N.	8	Neg.	70	110	63	Neg.	Neg.	
W	F	20	Clear	N.	5	Neg.	68	90	75	Neg.	Neg.	
W	M	46	Clear	N.	2	Neg.	95	110	86	Neg.	Neg.	
			Clear	N.	3	Neg.	85	110	77	Neg.	Neg.	
			Clear	N.	2	Neg.	80	100	80	Neg.	Neg.	After intravenous injection of typhoid vaccine at intervals of four days for four weeks
W	M	28	Clear	N.	4	Neg.	80	105	76	Neg.	Neg.	
W	F	19	Clear	N.	5	Neg.	78	100	78	Neg.	Neg.	
Average (6 cases).....							79	106	75			

* Ratio of spinal fluid sugar to blood sugar.

TABLE 7.—*Combined Sclerosis*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Quickenstedt Reaction	Comment
W	M	60	Clear	N.	3	Neg.	70	105	66	Neg.	Neg.	Pernicious anemia
W	F	34	Clear	N.	5	Neg.	72	106	67	Neg.	Neg.	Sprue
W	F	35	Clear	N.	3	Neg.	90	108	83	Neg.	Neg.	Pellagra
W	M	32	Clear	N.	3	Neg.	80	110	72	Neg.	Neg.	Pellagra
W	M	49	Clear	N.	6	Neg.	75	100	75	Neg.	Neg.	Pernicious anemia
W	F	38	Clear	N.	4	Neg.	70	104	66	Neg.	Neg.	Pernicious anemia
W	M	36	Clear	N.	5	Neg.	80	110	72	Neg.	Neg.	Pellagra
Average (7 cases).....							77	106	72			

* Ratio of spinal fluid sugar to blood sugar.

Six patients with epilepsy also showed a tendency to high values, with an average of 88 mg. of sugar in the spinal fluid and a ratio of 79 per cent (table 10).

Increased intracranial pressure as a cause of high values for sugar in the spinal fluid is not supported by the data on thirteen patients with tumor of the brain. The average amount of sugar in the spinal fluid was 84 mg. and the average amount in the blood was 111 mg. The

TABLE 8.—*Diabetes Mellitus*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	F	40	Clear	N.	3	Neg.	275	330	83	Neg.	Neg.	Before treatment
C	F	54	Clear	N.	1	Neg.	240	300	80	Neg.	Neg.	Before treatment
			Clear	N.	2	Neg.	150	200	75	Neg.	Neg.	Insulin and diet
			Clear	N.	1	Neg.	120	170	70	Neg.	Neg.	
C	F	17	Clear	N.	6	Neg.	240	280	85	Neg.	Neg.	Before treatment; no complications
W	M	40	Clear	N.	3	Neg.	80	118	67	Neg.	Neg.	Under control
W	M	55	Clear	N.	48	+1	85	130	65	+4	Neg.	Paresis; diabetes
Average (5 cases).....							170	218	75			

* Ratio of spinal fluid sugar to blood sugar.

TABLE 9.—*Nervous and Mental Group*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	25	Clear	N.	4	Neg.	76	108	70	Neg.	Neg.	Dementia praecox
W	F	26	Clear	N.	3	Neg.	78	102	76	Neg.	Neg.	Hysteria
W	F	23	Clear	N.	2	Neg.	85	96	88	Neg.	Neg.	Hysteria
W	F	27	Clear	N.	3	Neg.	82	120	68	Neg.	Neg.	Hysteria
W	M	22	Clear	N.	3	Neg.	80	90	88	Neg.	Neg.	Dementia praecox
W	F	22	Clear	N.	3	Neg.	88	107	82	Neg.	Neg.	Moron
W	M	15	Clear	N.	2	Neg.	94	114	82	Neg.	Neg.	Dementia praecox
W	M	40	Clear	+2	4	Trace	100	110	90	Neg.	Neg.	Paranoia with basal metabolism +17 per cent
W	F	44	Clear	N.	4	Neg.	75	104	72	Neg.	Neg.	Dementia praecox; morphinism
W	M	19	Clear	N.	1	Neg.	86	105	80	Neg.	Neg.	Moron
Average (10 cases).....							84	106	79			

* Ratio of spinal fluid sugar to blood sugar.

TABLE 10.—*Epilepsy*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	13	Clear	N.	366	+3	80	102	78	Neg.	Neg.	Twenty-four hours after convulsion
			Clear	N.	36	Trace	85	100	85	Neg.	Neg.	Nine days after convulsion
W	F	18	Clear	N.	6	Neg.	84	102	82	Neg.	Neg.	No recent convulsion
W	F	16	Clear	N.	1	Neg.	100	110	90	Neg.	Neg.	Puncture not made after recent convulsion
W	F	24	Clear	N.	3	Neg.	88	105	83	Neg.	Neg.	No recent convulsion
C	F	14	Clear	+2	5	Neg.	100	160	62	Neg.	Neg.	Puncture followed 48 hours of continuous convulsions
W	M	34	Clear	N.	1	Neg.	80	104	77	Neg.	Neg.	No recent convulsions
Average (6 cases).....							88	112	79			

* Ratio of spinal fluid sugar to blood sugar.

TABLE 11.—*Tumor of the Brain*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	23	Clear	+3	4	Neg.	86	112	76	Neg.	Neg.	Right frontal tumor
W	F	27	Clear	N.	8	Neg.	75	100	75	Neg.	Neg.	Suspected cerebellar tumor
W	F	37	Clear	+1	47	Trace	90	108	83	Neg.	Neg.	Pituitary tumor
W	F	60	Clear	N.	3	Neg.	90	130	69	Neg.	Neg.	Pituitary tumor
W	M	3	Clear	+2	3	Neg.	80	105	76	Neg.	Neg.	Cerebellar tumor
W	M	54	Clear	+1	8	Neg.	78	115	67	Neg.	Neg.	Right frontal tumor
W	F	44	Clear	N.	4	Neg.	68	98	69	Neg.	Neg.	Right frontal tumor
W	M	43	Clear	+4	3	Neg.	90	100	90	Neg.	Neg.	Left parietal endothelioma
W	F	13	Clear	N.	3	Neg.	90	115	77	Neg.	Neg.	Left parietal tumor
W	F	45	Clear	+1	2	Neg.	73	112	65	Neg.	Neg.	Tumor medulla
W	M	51	Clear	+1	8	Neg.	86	100	86	Neg.	Neg.	Left frontal tumor
W	M	23	Clear	+3	4	Neg.	86	112	76	Neg.	Neg.	Right frontal tumor
W	F	43	Clear	N.	1	Neg.	100	130	76	Neg.	Neg.	Glioma in left frontal lobe
Average (13 cases).....							84	111	76			

* Ratio of spinal fluid sugar to blood sugar.

highest individual reading for sugar in the spinal fluid was 100 mg., but this was only 76 per cent of the amount of sugar in the blood (table 11).

Nineteen patients presenting no neurologic condition gave an average of 89 mg. of sugar in the spinal fluid and a ratio of 76 per cent (table 12).

TABLE 12.—*Cases Presenting No Neurologic Condition*

Race	Sex	Age, Years	Appearance of Cerebrospinal Fluid	Pressure of Cerebrospinal Fluid	Cells	Globulin	Spinal Fluid Sugar, Mg.	Blood Sugar, Mg.	Ratio, per Cent*	Wassermann Reaction	Queckenstedt Reaction	Comment
W	M	60	Clear	N.	1	Neg.	90	120	75	Neg.	Neg.	Hypertension
C	M	14	Clear	N.	5	Neg.	90	112	80	Neg.	Neg.	Appendical abscess
C	M	38	Clear	N.	1	Neg.	85	115	73	Neg.	Neg.	Rectal stricture
W	M	37	Clear	N.	1	Neg.	80	95	83	Neg.	Neg.	Pulmonary tuberculosis
C	F	18	Clear	N.	6	Neg.	120	210	57	Neg.	Neg.	Influenzal pneumonia
C	F	20	Clear	N.	11	Trace	90	108	83	Neg.	Neg.	Mild hyperthyroidism
W	M	19	Clear	N.	3	Neg.	105	132	79	Neg.	Neg.	Malaria; puncture not made after a chill
C	M	50	Clear	N.	3	Neg.	88	104	84	Neg.	Neg.	Essential hypertension
C	M	48	Clear	N.	2	Neg.	88	100	88	Neg.	Neg.	Chronic arthritis
C	M	38	Clear	N.	2	Neg.	90	118	76	Neg.	Neg.	Hypertension
W	M	50	Clear	N.	2	Neg.	88	112	78	Neg.	Neg.	Pellagra; morphinism
W	M	40	Clear	N.	2	Neg.	85	130	65	Neg.	Neg.	Splenic anemia
C	M	41	Clear	N.	2	Neg.	90	104	85	Neg.	Neg.	Malaria and frontal headache
W	F	40	Clear	N.	2	Neg.	76	115	66	Neg.	Neg.	Myxedema
C	M	45	Clear	N.	2	Neg.	80	104	77	Neg.	Neg.	Pulmonary tuberculosis; chronic alcoholism
W	M	25	Clear	N.	1	Neg.	85	110	77	Neg.	Neg.	Chronic tonsillitis; malaise; headache
W	F	38	Clear	N.	2	Neg.	88	100	88	Neg.	Neg.	Myxedema with paranoid background
W	F	28	Clear	N.	4	Neg.	80	100	80	Neg.	Neg.	Chronic endometritis
W	F	21	Clear	+1	1	Neg.	102	120	85	Neg.	Neg.	Influenza; no evidence of encephalitis
Average (19 cases).....							89	116	76			

* Ratio of spinal fluid sugar to blood sugar.

CONCLUSIONS

1. The ratio of the sugar in the spinal fluid to the sugar in the blood in this series of cases is higher than most of the values previously recorded. Similar results were obtained by different methods of titration.

2. A high reading for sugar in the spinal fluid is not in itself diagnostic of any given disease.

3. Table 6 shows the necessity of determining the amount of sugar in the blood simultaneously with the amount of sugar in the spinal fluid and making these readings after the patient has fasted for twelve hours.

4. In tuberculous and purulent meningitis, the sugar in the spinal fluid decreases as the disease progresses.

5. Determination of the sugar in the spinal fluid aids in the differential diagnosis of some neurologic conditions that may have similar clinical pictures, such as epidemic encephalitis and meningitis.

NATIVE COMPLEMENT IN HYPERTHYROIDISM*

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In this communication I shall attempt to answer the question as to whether or not native complement is increased in the blood serum in hyperthyroidism, and I shall discuss the relationship between the complement value as determined by hemolytic titration and the basal metabolic rate as determined by indirect calorimetry.

This study was suggested by the recent work of Hadjopoulos and Burbank [1] on the rôle of complement in health and disease. These investigators demonstrated that complement varies considerably from the normal in the course of acute infections, and that this variation is of prognostic value. They found complement increased in hyperthyroidism and decreased in hypothyroidism: "Known pathologic conditions that give rise to high metabolism such as hyperthyroidism were also found by us to give a high complement titre while the reverse was found true in true hypothyroidism . . ." On the basis of this research, Hadjopoulos and Burbank proposed a new theory concerning the origin and nature of complement. They advanced the hypothesis that complement is a catabolic product elaborated in greater or less quantities during metabolic activity in a proportion required by the animal economy. They assumed that complement is of protein nature or a product of protein cleavage. This theory, original in its conception, is no less speculative than the various theories prevalent during the past quarter of a century, which formed the basis of sharp controversy between the German and French schools of immunology.

Metchnikoff [2] and his followers, principally supported by Gengou, were firmly convinced that complement (addiment) belongs to the category of cytases or soluble ferments and is an intracellular or fixed substance of the leukocytes (phagocytes). On the basis of their researches, Metchnikoff stated that complement is not free in the circulating blood, but that its presence in the serum of mammalian blood in vitro is due unquestionably to grave injury or destruction of the leukocytes produced during the withdrawal and subsequent clotting of the blood. He, therefore, denied the presence of free complement in the circulating blood.

* Submitted for publication, Dec. 16, 1930.

* From the Laboratories of the Diagnostic Center, U. S. Veterans Hospital, Washington, D. C.

1. Hadjopoulos, L. G., and Burbank, R.: J. Lab. & Clin. Med. **14**:131 (Nov.) 1928.

2. Metchnikoff, Eli: Natural Immunity in Infective Disease, translated by Francis G. Binni, London, Cambridge University Press, 1905.

Buchner,[3] theoretically agreeing that alexin is of leukocytic origin and in the nature of a ferment, held that complement is a leukocytic secretion. This contention brings up the possibility that complement is free in the circulating blood.

Ehrlich [4] maintained, contrary to Metchnikoff's contention, that complement is free in the circulating blood and not dependent on leukocytic destruction for its presence in the serum; also that several complements, or what is spoken of as multiplicity of complement, exist.

Gurd [5] expressed the belief that complement does not exist in the blood as such but in the form of a complementogen, and that it is activated by some substance in the leukocytes.

Zinsser [6] conceded the fact that injury to the cells may be a factor in the production of complement, but he stated the belief that complement is free in the circulating blood. He said: "Considering the very probable participation of alexine in opsonic functions, this (injection of bacteria into a living animal and finding a very rapid and active phagocytosis) would seem to point very strongly towards the presence of this substance in the circulating blood."

Kolmer [7] expressed the opinion that complement resides in the globulin fraction of the serum protein or perhaps is carried along with the former, and that it is probably enzymic in nature.

Hyde [8] has recently, by ingenious experiments on the frog, thrown some doubt on the contention that complement is intraleukocytic and bound. He inoculated copiously washed sheep cells intrapericardially into the frog, and for several hours made microscopic observations of the integrity and movement of these cells. During this period they were intact and uninjured. When rabbit sensitizer (amboceptor) was subsequently injected into the frog, the sheep cells were hemolyzed and could not be seen in the circulation. Hyde thought that this was an in vivo experiment conceding the possibility of leukocytic injury during the process of intrapericardial injection.

Hyde [9] has also shown by his work on the plasma of a hemophiliac that the complementary property of this plasma is as potent as that of the serum obtained after retarded clotting, and that its potency is comparable to that of normally clotted blood serum. He expressed the

3. Buchner, quoted by Metchnikoff (footnote 2, p. 189).

4. Ehrlich, P., quoted by Metchnikoff (footnote 2, p. 297).

5. Gurd, quoted by Hyde, Roscoe R (reference 8).

6. Zinsser, Hans: Infection and Resistance, ed. 3, New York, The Macmillan Company, 1923.

7. Kolmer, John F.: Serum Diagnosis by Complement Fixation, Philadelphia, Lea & Febiger, 1928.

8. Hyde, Roscoe R.: The Complementing Properties of Blood Plasma, Am. J. Hyg. **8**:859 (Nov.) 1928.

9. Hyde, Roscoe R.: The Complement Deficient Guinea-Pig, Am. J. Hyg. **7**:619, 1927.

belief that this plasma is as nearly natural as is obtainable and quite different from artificial plasma.

D'Herelle [10] took an extreme view regarding the entity of complement, a view perhaps not altogether fantastic. Complement itself "is an artificial principle, a product of the laboratory."

The foregoing brief review cites the fundamental controversial points regarding the mysterious origin and nature of complement. In this study it was not my object to solve the problem of the origin of complement; rather it was hoped that the determination of an increase of complement in the blood serum in hyperthyroidism would be of practical diagnostic importance and would supplement the evidence obtained through the basal metabolic rate.

It was necessary to assemble a group of normal controls in whom enlargement of the thyroid gland was not suspected and in whom the basal metabolic rate was within normal limits. It was equally necessary to study the variation in the titer of the hemolytic complement of normal subjects during consecutive daily periods. Additional controls on pathologic and well defined diseases were included.

TABLE 1.—*Grouping of Cases Selected for Study*

Normal controls	80
Normal controls (basal metabolic rate within normal limits)	30
Hyperthyroidism (unclassified)	31
Miscellaneous pathologic conditions	30
The latter group is made up as follows:	
Diabetes mellitus (uncomplicated mild type)	10
Pulmonary tuberculosis	8
Neurosyphilis	7
Nephritis (chemical analysis of the blood: nonprotein nitrogen, 66; urea nitrogen, 35; uric acid, 7.2 mg.)	1
Secondary anemia (red cells, 2,400,000; hemoglobin, 22%)	1
Myelogenous leukemia (white cells, 175,000 and 179,000)	1
Acute arthritis and diabetes (blood sugar, 200 mg; carbon dioxide, 22% by volume)	1
Huntington's chorea	1
Total cases	171
Total determinations (titrations)	262

In table 1 is shown the grouping of cases selected for this study. It includes a group of cases of miscellaneous diseases, citing laboratory observations that appeared pertinent to the study. One case of myelogenous leukemia is included in which the white blood cell counts at the time complement was determined are given.

The so-called average normal titer of complement in human serum is not a fixed quantity that would hold good and be reliable for comparative studies in the hands of every investigator. It depends primarily on the strength of the sheep cell suspension, used as the hemolytic indicator, and on the period of incubation. It also depends on the method of carrying out the titration, whether it is direct or whether diluted serum is used. The terminology for expressing the titer also

10. d'Herelle, F.: Immunity in Natural Infectious Diseases, English ed. by George H. Smith, Baltimore, Williams & Wilkins Company, 1924.

varies. That complement is variable in the serum of different animal species is well known; not only is it variable in different species of animals, but it varies in different animals of the same species. The cause of the variability of complement is not known. It is commonly assumed that diet plays a considerable rôle in the potency of, for instance, guinea-pig complement.

Regarding the variation of complement in human serum, in 700 specimens of blood from hospital patients, Hyde [3] found the average titer to be about 30 units. In only 1 per cent of his cases was the complement titer as high as 80 units, while in 2 per cent of the cases complement was not demonstrable. Hadjopoulos and Burbank [1] stated that in 2,000 cases studied by them, the average normal titer was found to be 0.04 cc. of active serum. My study confirms the observations of Hyde in that extremely high and extremely low titers for the complement of human serum were infrequent.

METHOD

An antisheep rabbit hemolytic serum was used, and since human complement was the quantitative factor sought, the amboceptor was adjusted against a pooled human serum (from five normal persons), an arbitrary 10 per cent dilution being used. The unit of the amboceptor thus determined was doubled and used as a constant in subsequent test titrations. During the progress of this work, approximately seven months, the amboceptor was kept in the icebox at about 8 C. and was occasionally checked. The sheep cell suspension used was 2.5 per cent, freshly prepared, washed and sensitized for ten minutes at the same icebox temperature. The serum tested for complement was carefully pipetted with a certified pipet into a series of tubes in graded amounts, beginning with 0.005 cc. and increasing to 0.05 cc. or a lower dilution was used if required. Physiologic solution of sodium chloride was added to each tube, bringing the volume to 0.6 cc. This was followed by incubation in a water bath at 37.5 C. for five minutes. Subsequently 0.4 cc. of a sensitized sheep cell mixture, consisting of equal volumes of the 2.5 per cent sheep cell suspension and 2 units of amboceptor, was added, and a final incubation for fifteen minutes in a water bath at 37.5 C. was allowed. The entire volume in each tube was 1 cc., and the final strength of the sheep cell suspension, 0.5 per cent. The results were read immediately after the period of incubation, and the tube containing the least amount of serum showing complete hemolysis was recorded as the titer of that serum. The tube showing almost complete hemolysis was recorded as 3+. The absorption of native amboceptor, while desirable, was not resorted to, since for comparative studies, this factor did not appear to be of great significance. The serums, with the exception of a few controls, were obtained at 2:30 p. m., kept at room temperature for one and a half hours, the clot being allowed to retract, and subsequently placed in the icebox until the next afternoon. When the serums were tested they were approximately twenty-four hours old, during which period they had been kept in contact with the clot.

RESULTS

The accompanying charts are graphic reproductions of the complement titer as recorded immediately after the fifteen minutes of incuba-

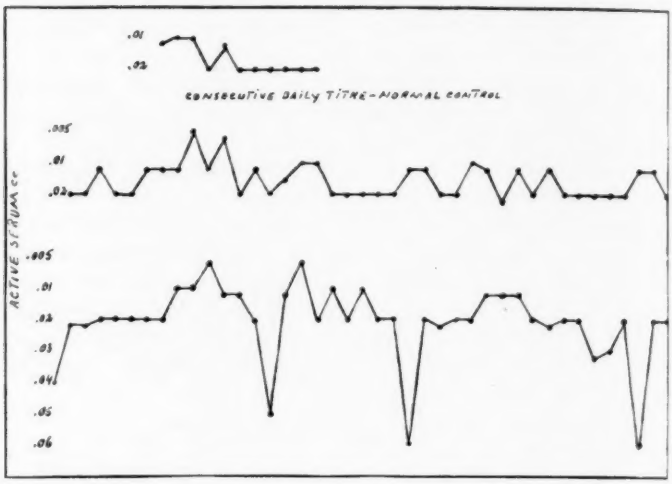

Chart 1.—Graph of the complement titer in normal controls.

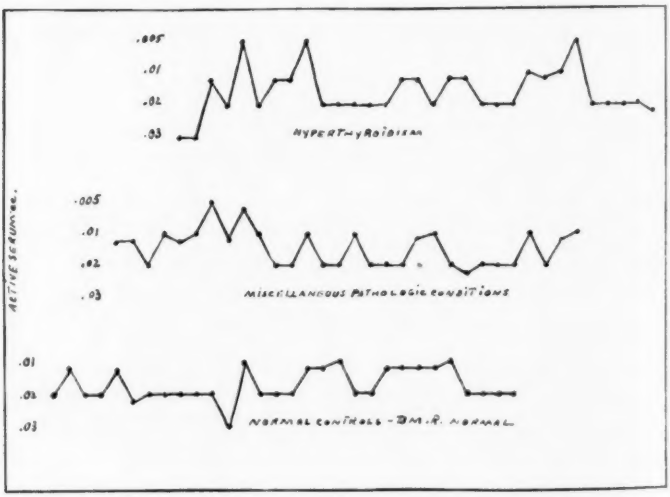

Chart 2.—Graph of the complement titer in normal controls and in patients with disease.

tion in the water bath at 37.5 C. A glance at the charts shows that there is a general topographic similarity in the curves. It is seen that the predominating complement titer in every group of cases is 0.02 cc. of active serum, that the next most frequent titer is 0.01 cc. or twice as high, and that a high titer of 0.005 cc. is extremely infrequent both in the general control group and in the control group in which the basal metabolic rate was normal. A low complement titer, such as 0.06 cc., or one three times as weak, is also infrequent.

In translating the charts into figures, it is noted that in the general normal control group of eighty cases, the range of 0.02 and nearly 0.02 cc. of active serum titer is furnished by forty-three cases, or 53 per cent; twenty-seven cases, or 33 per cent, fall into the range of 0.01 and nearly 0.01 cc. of active serum titer. A high titer of 0.005 cc. is given in four cases, or 5 per cent, and a very low titer in two cases, or 2.5 per cent. An approximately similar percentage of distribution of complement titer is seen in the normal control group in which the basal metabolic rate was within normal limits, namely, eighteen cases, or 60 per cent, furnished a titer of 0.02, and eleven cases, or 36 per cent, furnished a complement titer of 0.01 and nearly 0.01 cc. of active serum. No high titer was found in this group.

Comparing the titer of the controls with that of the group of thirty-one cases with hyperthyroidism it is found that sixteen cases, or 52 per cent, showed a titer of 0.02 cc., and that in ten cases, or 32 per cent, the complement titer was 0.01 cc. of active serum. Three cases of this group, or about 10 per cent, showed a high complement titer of 0.005, while two cases of the same group, or 6 per cent, furnished a titer of 0.03 cc.

It is thus seen that the incidence of variation in titer of the group with hyperthyroidism is strikingly similar to that of the normal control group. The incidence of a high complement titer associated with the typical basal metabolic rate is found in three cases, or about 10 per cent, as against four cases, or 5 per cent, in the control group. It should be noted that in two of the three cases in the group with hyperthyroidism showing a high titer, the basal metabolic rate was also high (from +41 to +42). However, in the face of the evidence presented, it would seem possible that the simultaneous high complement titer with a high basal metabolic rate in the two cases noted might be considered a mere coincidence.

Reference to chart 2 (center figure), based on thirty cases of miscellaneous pathologic conditions, shows that fourteen cases, or 46 per cent, showed a complement titer of 0.01 and that a similar number furnished a titer of 0.02 cc. of active serum. Two cases of this group showed a high titer of 0.005, the highest titer recorded. It should be explained that the frequency of higher titer in this group is accounted

for by the group of diabetic patients included in it. This observation (higher titer in diabetes) is perhaps worthy of further investigation.

While it is fairly evident that, as a constant observation, an unusually high complement titer or a deviation in titer from the so-called average normal is not demonstrable in the serum of persons with hyperthyroidism, either as compared with normal controls or with patients having miscellaneous pathologic conditions, it was deemed essential, for conclusive evidence, to study the postoperative complement titer in hyperthyroidism and to compare it with the titer obtained in the same persons before thyroidectomy.

In table 2 are shown the preoperative and postoperative basal metabolic rates and the complement titer in nineteen cases. Analysis is possible in only eleven cases in which both the hemolytic titer and the

TABLE 2.—*Complement Titer and Basal Metabolic Rate Before and After Thyroidectomy*

	Preoperative		Postoperative		
Case	Basal Metabolic Rate, Plus	Complement Titer, Cc.	Basal Metabolic Rate	Complement Titer, Cc.	Blood Collected After Operation, Days
2.....	18	0.02*	+12	0.01	35
31.....	41	0.005*	+47	0.02	28
35.....	67	0.03	— 7	0.01	35
4.....	60	.....	—10	0.01*	50
109.....	38	0.02	— 5	0.02	14
79.....	63	0.02	— 5	0.02	14
93.....	..	.....	+ 5	0.02	21
33.....	57	.....	— 5	0.02	21
101.....	11	.....	+ 3	0.02	21
62.....	42	0.005*	+10	0.01*	..
2.....	47	.....	0	0.01*	21
73.....	14	0.02	+ 2	0.02	14
201.....	19	0.02	+ 1	0.01*	14
167.....	18	0.01*	+ 7	0.005*	7
159.....	15	0.02	—10	0.02*	14
192.....	46	0.01*	+ 1	0.01*	9
235.....	34	0.01*	....	0.01	4
243.....	45	0.02	....	.....	..
189.....	34	.....	....	0.01	7

* Nearly complete hemolysis.

basal metabolic rate are available. In the last column of the table, the period of postoperative collection of specimens is noted in seventeen cases. Two possible analyses are indicated: 1. The comparison of the postoperative titer of all the cases in this group except one with the larger group of cases of hyperthyroidism, the complement titer of which has already been compared with that of the normal controls. This analysis shows that approximately 50 per cent of the cases fall in the range of 0.02 cc. active serum—a percentage incidence not dissimilar either to the group with hyperthyroidism as a whole or to the general normal group. 2. The comparison of the preoperative and postoperative titer with relation to the basal metabolic rate. This analysis is possible in only eleven cases, from which it is seen that while in all the cases the basal metabolic rate has returned to normal following thyroidectomy,

no change in complement titer is noted in six cases, or approximately 55 per cent, while a higher titer is noted in four cases, or 36 per cent. A single exception is noted in case 31, in which the complement titer dropped from nearly 0.005 to 0.02. The basal metabolic rate in this case did not return to normal (this patient suffered from a bilateral goiter). No significance is noted in regard to the period of collection of the sample, ranging from four to fifty days after thyroidectomy.

From the data presented in table 2 it becomes increasingly difficult to associate the complement value in the blood serum in hyperthyroidism with the basal metabolic rate.

SUMMARY

This study was undertaken to ascertain the possibility of using the native complement value in the serum of patients with hyperthyroidism as a supplementary test in the diagnosis of hyperthyroidism. It was hoped that the adoption of such a laboratory procedure would rest on the determination of an increase in the complement titer of persons with hyperthyroidism and on its relation to the basal metabolic rate. In all, 110 controls were used, in 30 of whom the basal metabolic rate was normal, and in 80 of whom the basal metabolic rate was not suspected to have been abnormal.

CONCLUSIONS

The complement titer in normal controls, in the determination of which an antisheep rabbit hemolytic serum, a 2.5 per cent sensitized sheep cell suspension and incubation in the water bath at 37.5 C. for fifteen minutes were employed, was found to be 0.02 cc. of active serum in about 50 per cent of the cases. A titer of 0.01 is next in frequency in about 35 per cent of the cases. A high complement titer as well as a very low titer is infrequent.

No increase of complement value or significant deviation from the average normal range was found in a group of thirty-one unclassified cases of hyperthyroidism. A high titer (0.005) was found in three cases or 10 per cent, in two of which the basal metabolic rate was also high, which appears to be a mere coincidence.

The postoperative and preoperative complement value in the serum of patients with hyperthyroidism when compared with the postoperative and preoperative basal metabolic rates does not suggest any significant relationship. No change in titer was noted in 55 per cent of the cases, while a higher complement value was obtained in 36 per cent of the cases following thyroidectomy.

THE RESPIRATORY QUOTIENT

ITS USE IN THE DIAGNOSIS OF DIABETES MELLITUS *

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This article is best prefaced by the following excerpt from Joslin's book, "Treatment of Diabetes Mellitus." [1]

> It is convenient to classify patients with glycosuria or with a history of glycosuria into four groups: true diabetics, potential diabetics, renal glycosurics, and unclassified diabetics. Under true diabetics are placed patients whose blood sugar on an unrestricted diet is 0.14 per cent or more fasting, or 0.17 per cent or more after a meal with simultaneous glycosuria which is plainly related to diet. Potential diabetics are those with glycosuria closely related to the diet who easily become sugar-free with slight restrictions, but whose blood sugar is below 0.14 per cent fasting and never reaches 0.17 per cent after a meal. Renal glycosurics are individuals who have shown a constant glycosuria, irrespective of diet, for years, are symptomless, and have a blood sugar which is invariably normal. "Unclassified" diabetics by my nomenclature include the remaining cases of glycosuria, especially those associated with organic disease: for example, that of the gall-bladder, kidney, occasionally of the thyroid, cancer of the pancreas and often pregnancy.

In diabetes mellitus there is a disturbance in the metabolism of proteins and fats, as well as in that of carbohydrates, but from the standpoint of diagnosis it is sufficient to consider the metabolism of carbohydrates. This may be studied from the following standpoints: (1) the determination of the presence of glycosuria; (2) changes in the concentration of sugar in the blood, and (3) changes in the respiratory quotient. These points will be considered in the foregoing order. The first two will be studied cursorily and only in their relation to the main subject.

Diabetes mellitus means the passing through of sugar or glycosuria. It has been shown by John [2] and by others that the renal threshold for dextrose varies from 0.045 to 0.348 per cent of the sugar in the

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* Submitted for publication, Dec. 16, 1930.

* From the Departments of Metabolism and Pathology, and the Diabetic Clinic of the Jewish Hospital.

1. Joslin, E. P.: The Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928, p. 99.

2. John, H. J.: Differential Diagnosis of Diabetes by Means of Glucose Tolerance, J. A. M. A. **79**:1234 (Oct. 7) 1922.

blood. It is evident that a person with a low renal threshold may have marked glycosuria; this occurs in the cases of so-called renal glycosuria or diabetes innocens. It has also been convincingly shown by John [2] that, because the glycosuria is slight and transient, the presence of diabetes may remain unrecognized for a long time in persons with a high renal threshold and a moderately severe diabetes. Glycosuria may also occur when hyperglycemia is produced by conditions other than diabetes mellitus, such as nephritis, hyperthyroidism and hypertension. From the scientific standpoint the presence or absence of glycosuria is unimportant in the diagnosis of diabetes mellitus. The term "diabetes mellitus" is a misnomer and does not adequately describe the condition that is known by that name. The disease may more properly be termed hypo-insulinism. It parallels such terms as hypothyroidism and hypopituitarism.

An elevated fasting level for sugar in the blood indicates, in the vast majority of instances, the presence of diabetes mellitus. However, a high content of sugar in the blood may occur in other conditions, such as hyperthyroidism, nephritis and hypertension. Furthermore, as a result of restriction in carbohydrates in the diet of patients with diabetes mellitus, the sugar in the blood may be normal when the patient is fasting.

Valuable information may be obtained by studying the blood sugar curve after the ingestion of dextrose; this is the dextrose tolerance test. A normal blood sugar curve may be considered as one that (1) has a fasting level of from 0.7 to 1.1 Gm. per liter, (2) reaches its peak in one hour after the ingestion of dextrose (usually it reaches the peak earlier and rarely goes higher than 1.7 Gm.) and (3) tends to reach its fasting level within two hours, occasionally in three. In any case in which the curve is higher than normal, the possible presence of diabetes mellitus must be considered. It has been definitely established that a high blood sugar curve may occur in the following conditions: hypertension, nephritis, pregnancy, hyperthyroidism, hepatic disease and arthritis. As previously stated, Joslin described these as cases of "unclassified" diabetes. It appears to us that they may be more correctly called cases of unclassified hyperglycemia or glycosuria. This entire subject was clearly reviewed by Ohler.[3]

In a series of 160 cases who underwent glucose tolerance tests, glycosuria was absent with 103 and 57 showed only small amounts. Of the 103 cases without glycosuria, 37 gave normal glycemic reactions, 53 definitely abnormal, and 12 doubtful reactions; or in other words, 60 per cent of the cases without glycosuria gave abnormal sugar tolerance reactions. An analysis of the cases in this group shows that a very large percentage of the abnormal reactions were found in the

3. Ohler, W. R., quoted by Joslin (footnote 1, p. 212).

following pathological conditions (arranged in the order of frequency): gall-bladder disease; cirrhosis of the liver; bronchial asthma; arteriosclerosis; carcinoma; obesity; endocrine disturbance; chronic nephritis; chronic arthritis.

Of the 57 cases in which glycosuria was found, 9 gave perfectly normal reactions. These 9 fulfil all the requirements of so-called renal glycosuria. The remaining 48, or 84 per cent, showed definitely normal reactions, despite the fact that in every instance the fasting blood sugar was perfectly normal.

There exists, then, a group of cases, in which the foregoing method of procedure, namely, the use of the dextrose tolerance test, is inadequate in the determination of the absence or presence of diabetes mellitus.

THE CLASSIFICATION OF "UNDETERMINED" CASES

We come now to the consideration of the respiratory quotient and its use in classifying these "undetermined" cases.

The respiratory quotient of normal persons twelve hours after a meal was determined by Benedict, Emmes, Roth and Smith[4] and was found to be 0.83 for men and 0.81 for women. As a rule it is lower in persons with diabetes; the more severe the diabetes, the lower is the respiratory quotient. The respiratory quotient during fasting is lower in normal persons if they have been deprived of carbohydrate for several days. Conversely it was shown by Benedict, Emmes and Riche[5] that after an evening meal rich in carbohydrate, the respiratory quotient on the following day may be 0.88. It is seldom, however, that such great changes are encountered in the diet as were employed by these experimenters with their subjects. It has been shown by Bernstein and Falta[6] and others that the respiratory quotient after the administration of dextrose will not rise until an optimum percentage of glycogen in the liver is obtained. It is only after the glycogen depots have been filled that the oxidation of dextrose will commence. Consequently, in a person who has been on a diet poor in carbohydrate for several days, there will be a delay in the rise of the respiratory quotient; whereas when the body is surfeited with glycogen there will be an early rise, which to some extent must be attributed to the conversion of carbohydrate to fat. Gigon[7] found that in a normal person the respiratory quotient never rises before one-half hour after the

4. Benedict, F. G.; Emmes, L. E.; Roth, P., and Smith, H. M.: The Basal, Gaseous Metabolism of Normal Men and Women, J. Biol. Chem. **18**:139, 1914.

5. Benedict, F. G.; Emmes, L. E., and Riche, J. A.: The Influence of the Preceding Diet on the Respiratory Quotient After Active Digestion Has Ceased, Am. J. Physiol. **27**:383, 1911.

6. Bernstein, S., and Falta, W.: Respiratorischer Stoffwechsel und Blutzuckeregulation, Deutsches Arch. f. klin. Med. **125**:233, 1918.

7. Gigon, quoted by Bornstein and Holm (footnote 8).

administration of dextrose. Indeed, Bornstein and Holm [8] found that the respiratory quotient may actually fall during the first fifteen minutes and suggesed that this may be due to the retention of carbon dioxide in the body for the purpose of combining with alkali released by the secretion of acid in the gastric juice.

In diabetes mellitus there is a deficiency in glycogenesis and in the storage of glycogen. The question whether there is also a diminution in the ability to oxidize dextrose is still in a polemic state. Macleod [9] stated: "The occurrence of these low quotients and their failure to respond to ingestion of glucose are often cited as evidence that the tissues in diabetes have lost the power to oxidize carbohydrates but there is no direct evidence that this is really so." Joslin [10] expressed the belief that the person with diabetes can burn sugar if the sugar can first be transformed into glycogen. But since a fundamental feature of diabetes mellitus is the inability to form glycogen, then indirectly there is a diminution in the oxidation of dextrose. This may be accepted as incontrovertible: In diabetes mellitus the respiratory quotient during fasting is lower than the normal quotient, and the respiratory quotient curve fails to rise to a normal level after the ingestion of dextrose. A low respiratory quotient curve indicates a deficiency of insulin or the neutralization or inactivation of an adequate supply of insulin.[11] The converse is true, namely, that a normal respiratory quotient curve indicates an adequate supply of insulin.

The question to be considered now is: What constitutes a normal respiratory quotient curve? It is to be deplored that so little work has been done to put this subject on a firm basis. It is fallacious to take as a standard the amount of dextrose oxidized in a certain period, even if calculated per square meter of surface area, for the reason that the amount of active tissue in the body cannot be determined. The important feature is this: When suddenly flooded with dextrose, the normal body will oxidize it in preference to fat. The figure determined for the respiratory quotient during fasting is unimportant. The

8. Bornstein, A., and Holm, K.: Ueber den respiratorischen Stoffwechsel bei alimentärer Glykämie, Biochem. Ztschr. **130**:209, 1922.

9. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 6, St. Louis, C. V. Mosby Company, 1930, p. 912.

10. Joslin, E. P. (footnote 1, p. 103).

11. This does not include phlorizin diabetes in which the respiratory quotient rises only slightly after the administration of dextrose. This is the result, not of the inability of the organism to oxidize dextrose, but of the rapid elimination of dextrose by the kidney. It is conceivable that in renal glycosuria if the threshold is markedly low and the excretion of dextrose extremely high, the respiratory quotient might fail to rise to the normal level after the administration of dextrose. To our knowledge no such case has been reported.

important point is: What is the ratio of the amount of fat to the amount of carbohydrate oxidized two or three hours after the ingestion of dextrose? Rabinowitch [12] stated that a rise of 0.12 in the respiratory quotient may be considered normal. This is the average for a group of cases, but cannot be applied to an individual case. If the respiratory quotient during fasting is 0.71, a rise to 0.83 cannot be considered normal. It goes without saying that during fasting a rise in the respiratory quotient from 0.84 to 0.90 cannot be called abnormal. From our own observations and from those of Sanger and Hun [13] and Bornstein and Holm,[8] we have come to the conclusion that the respiratory quotient must rise to 0.88 within two and one-half hours in order to be considered normal.[14]

It was previously stated that if a high blood sugar curve is present, the presence of diabetes mellitus must be suspected. This dilemma

TABLE 1.—*Curves of Respiratory Quotient in Normal Controls (Sanger and Hun)*

	Respiratory Quotient	30 Minutes*	60 Minutes	90 Minutes	120 Minutes	150 Minutes	Range
C. L.	0.78	0.82	0.80	0.89	0.87	0.94	0.16
H. D.	0.83	0.81	0.80	0.88	0.88	0.90	0.09
W. U. G.	0.75	0.84	0.88	0.88	0.84	0.90	0.15
E. H.	0.77	0.80	0.80	0.90	0.92	0.90	0.15
B. S.	0.78	0.80	0.84	0.86	0.88	0.86	0.10
M. C.	0.79	0.82	0.88	0.89	0.92	0.93	0.14
M. C.	0.83	0.83	0.86	0.83	0.92	0.90	0.09
H. J.	0.85	0.83	0.84	0.88	0.93	0.89	0.10
R. Mc.	0.83	0.88	0.84	0.88	0.93	0.92	0.10
H. R. Q.	0.75	0.79	0.81	0.86	0.83	0.87	0.12
Average	0.80	....	....	....	....	....	0.12

* 1.75 Gm. of dextrose per kilogram of body weight.

occurs particularly in cases of hyperthyroidism, hypertension and other conditions already mentioned. It was shown by Sanger and Hun [13] that the respiratory quotient curve is normal in hyperthyroidism. Similar observations have been made by us [15] in hypertension and by Linder, Hiller and Van Slyke [16] in nephritis. If diabetes mellitus complicates these conditions, it will make itself evident by a low respiratory quotient curve.

12. Rabinowitch, I. M.: Simultaneous Respiratory Exchange and Blood Sugar Time Curves Obtained in Diabetic and Non-Diabetic Individuals Following Ingestion of Glucose, J. Clin. Investigation **2**:143, 1925.

13. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

14. Sanger and Hun, as well as we, employed 1.75 Gm. of dextrose per kilogram of body weight. Bornstein and Holm gave 100 Gm. per patient.

15. Wishnofsky, M., and Byron, C. S.: Carbohydrate Metabolism in Hypertension, Arch. Int. Med. **47**:790 (May) 1931.

16. Linder, G. C.; Hiller, A., and Van Slyke, D. D.: Carbohydrate Metabolism in Nephritis, J. Clin. Investigation **1**:247, 1925.

REPORT OF CASES

We shall present four cases (two of hyperthyroidism and two of hypertension) in which the respiratory quotient curve was the sole factor determining the nature of the disturbance in the metabolism of carbohydrates.

The essential features of the first two cases (hyperthyroidism) are as follows:

CASE 1.—J. A., a housewife, aged 49, had experienced tremors, palpitation, weakness, choking sensations, nervousness and profuse perspiration for the past two or three years. Her weight during this period was reduced from 175 to 170 pounds (79.4 to 77.1 Kg.), a loss of 5 pounds (2.3 Kg.).

There was a freely movable nodule as large as a walnut in the isthmus of the thyroid gland. The blood pressure was markedly labile (230 systolic and 110 diastolic on Sept. 19, 1929, and 110 systolic and 80 diastolic on March 19, 1930). During the interval the systolic blood pressure was usually 170 or 190. The urine,

TABLE 2.—*Curves for Blood Sugar and Respiratory Quotient in Two Cases of Hyperthyroidism*

	Case 1 (J. A.)		Case 2 (R. B.)	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	156*	0.763	115	0.75
45 minutes†	272	.....	282	....
75 minutes	...	0.850	...	0.75
120 minutes	272	.....	277	....
135 minutes	...	0.883	...	0.83

* Milligrams in 100 cubic centimeters of blood.
† 1.75 Gm. of dextrose per kilogram of body weight.

examined on Aug. 22, 1928, Sept. 21, 1929, and March 21, 1930, was negative for sugar. The patient was on an unrestricted diet. The basal metabolic rate was plus 36 per cent on March 21, 1930.

CASE 2.—R. B., a housewife, aged 40, had experienced headache, dizziness, insomnia, palpitation and loss of weight (50 pounds [22.7 Kg.]) during the past two years. She stated that glycosuria was discovered one year previously.

Physical examination showed: diffuse enlargement of the thyroid gland; pulse rate, 124; blood pressure, 140 systolic and 70 diastolic; basal metabolism, plus 65 per cent. The blood sugar on May 6, 1929, was 0.166, and on Oct. 4, 1929, 0.157 per cent.

A simultaneous study of the blood sugar curve and the respiratory curve was made. Each patient after fasting fourteen hours received 1.75 Gm. of dextrose per kilogram of body weight. Three specimens of venous blood were taken from each patient: one at the "fasting level," and two at intervals of forty-five minutes and two hours after ingestion, respectively. The sugar content of the blood was determined by the Folin-Wu method. The respiratory quotient was determined at the "fasting level," and at intervals of one and one-quarter and two and one-quarter hours after ingestion, respectively. These intervals were chosen after careful consideration as best describing the nature of the curve. The gas was collected in a Tissot spirometer and analyzed by the method of Henderson and Haldane. The results are incorporated in table 2.

It will be noted that both cases showed "diabetic" blood sugar curves which were practically identical except that in case 2 the fasting level was only 115. Previous examinations, however, gave values above 150. Case 2 gave a history of glycosuria, whereas at no time was sugar found in the urine in case 1. It was postulated by one of us (M. W.[17]) that the blood sugar curve is the best index of the severity of diabetes mellitus. If both patients were diabetic the cases were of equal severity. The presence or absence of glycosuria is simply incidental to the renal threshold.

Since both patients suffered from hyperthyroidism, and as it has been abundantly shown that a high blood sugar curve occurs in a majority of such cases, it remained for the respiratory quotient curve to decide the nature of the disturbance in the metabolism of carbohydrates. It will be observed that in case 2 there was a low respiratory

TABLE 3.—*Curves for Blood Sugar and Respiratory Quotient in Two Cases of Hyperthyroidism*

	Case 3 (T. S.)		Case 4 (J. W.)	
	Blood Sugar	Respiratory Quotient	Blood Sugar	Respiratory Quotient
Fasting level	133*	0.753	111	0.795
45 minutes†	205	.....	214	.....
75 minutes	...	0.856	...	0.925
120 minutes	187	.....	172	.....
135 minutes	...	0.848	...	0.903

* Milligrams in 100 cubic centimeters of blood.
† 1.75 Gm. of dextrose per kilogram of body weight.

quotient curve, whereas in case 1 the curve was normal. This study gave scientific proof that in case 2 the disturbance in the metabolism of carbohydrates was diabetic and that in case 1, nondiabetic.

A similar study was performed in two cases of hypertension. Practically all cases of hypertension show a high blood sugar curve, but the respiratory quotient curve is normal.[15] They are therefore cases neither of potential nor of mild diabetes. Any case of mild diabetes among them can be determined only by a study of the respiratory quotient curve. This is well illustrated by table 3.

The patients in cases 3 and 4 were women, past 40, who had been suffering from hypertension (systolic blood pressure above 170 mm. of mercury) for several years. At no time had dextrose been detected in the urine. It will be observed that both had high blood sugar curves. Whereas the respiratory quotient curve in case 4 was above normal,

17. Wishnofsky, M.: The Use of the Dextrose Tolerance Test in the Determination of the Severity of Diabetes Mellitus, Arch. Int. Med. **42**:443 (Sept.) 1928.

that in case 3 was below normal. The disturbance in the metabolism of carbohydrate, shown in case 4, may therefore be considered to be nondiabetic; case 3, however, may be considered to be a potential or mild diabetes.

It is evident that the ultimate criterion in the determination of the presence of diabetes mellitus is the study of the respiratory quotient curve.

SUMMARY AND CONCLUSIONS

The disturbance in the metabolism of carbohydrates may be considered from three standpoints: the determination of the presence of glycosuria, changes in the concentration of sugar in the blood and changes in the respiratory quotient.

The renal threshold for dextrose varies from 45 to 348 mg. per hundred cubic centimeters of blood. Glycosuria occurs in persons with a low renal threshold who are not diabetic. A diabetic person with a high threshold may have transient glycosuria or none.

A high level of sugar in the blood during fasting, and especially a high blood sugar curve after the ingestion of dextrose, may occur in conditions other than diabetes, such as hypertension, nephritis and hyperthyroidism.

From the scientific standpoint, the presence of glycosuria and hyperglycemia is inadequate for the diagnosis of diabetes mellitus.

A respiratory quotient curve that rises to 0.88 after the ingestion of an adequate amount of dextrose is indicative of a normal secretion of insulin; a low respiratory quotient curve, with certain exceptions, indicates a diminution in the secretion of insulin, or a neutralization or inactivation of an adequate supply.

In a study of both the blood sugar and the respiratory quotient curves after the ingestion of dextrose in two cases of hyperthyroidism and two of hypertension, it was demonstrated that the ultimate criterion in the diagnosis of diabetes mellitus is the respiratory quotient curve.

THE SIGNIFICANCE OF THE POTASSIUM-CALCIUM RATIO AND OF THE INORGANIC PHOSPHORUS AND CHOLESTEROL OF THE BLOOD SERUM IN ARTERIAL HYPERTENSION *

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The most significant abnormal feature of arterial hypertension, in the light of present knowledge, is the increased peripheral arteriolar resistance. Weiss and Ellis,[1] in 1930, attempted to measure the peripheral resistance quantitatively, and found that the average resistance of the arteriolar system of the greater circulation in a group of patients with hypertension was twice as great as in the normal control subjects. The factors, however, that are responsible for this increase in arteriolar resistance were not established.

The work of a number of investigators, such as Billigheimer,[2] Kraus and Zondek,[3] Zondek,[4] Kylin [5] and Spiro,[6] indicated that the increased peripheral constriction of the vascular system is due to a disturbance of the vegetative nervous system. This altered function of the autonomic nervous system, according to these investigators, is accompanied by a change in the equilibrium of the blood through two powerful physiologic

* Submitted for publication, Dec. 20, 1930.

* From the Thorndike Memorial Laboratory, the Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine of the Harvard University Medical School.

* This investigation was aided by a grant from the Ella Sachs Plotz Foundation given in honor of Francis W. Peabody.

1. Weiss, S., and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, Am. Heart J. **5**:448, 1930.

2. Billigheimer, E.: Der Calciumspiegel im Blute und seine Beeinflussung durch verschiedene Gifte, Klin. Wchnschr. **1**:256, 1922.

3. Kraus, F., and Zondek, S. G.: Ueber die Durchtränkungsspannung, Klin. Wchnschr. **1**:1773, 1922.

4. Zondek, S. G.: Die Bedeutung des Antagonismus von Kalium und Calcium für die Physiologie und Pathologie, Klin. Wchnschr. **2**:382, 1923.

5. Kylin, E.: Der Gehalt des Blutes an Calzium und Kalium, Acta med. Scandinav., 1927, supp. 19, p. 1.

6. Spiro, P.: Klinische Untersuchungen über das Calcium-Kalium-Gleichgewicht im Organismus, Ztschr. f. klin. Med. **110**:58, 1929.

agents, potassium and calcium, with an increase in potassium, a decrease in calcium, and thus an increase in the potassium-calcium ratio. Other investigators, however, including Westphal,[7] expressed the belief that changes in the osmotic relationships and permeability of the capillary bed and tissues, due to an increase in serum cholesterol, are responsible for elevated blood pressure.

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE POTASSIUM-CALCIUM RATIO AND ITS RELATION TO THE AUTONOMIC NERVOUS SYSTEM AND THE ARTERIAL BLOOD PRESSURE

The theory that a change in the potassium content of the blood and the tissue fluids may influence the height of the blood pressure is supported by experimental observation. Mathison[8] showed that potassium salts injected intra-arterially produce a rise in blood pressure. He also studied the effect of calcium in antagonizing the action of potassium on the blood pressure of spinal animals, and found that when equimolar quantities of potassium chloride and calcium chloride were injected intra-arterially, the blood pressure rose only slightly. He concluded that an increase in calcium tends to diminish the blood pressure, but that its action is not as pronounced as that of potassium in increasing the pressure. Harrison, Pilcher and Wilson[9] observed no change in the cardiac output of dogs following the intravenous injection of potassium salts into the circulation. Chiari and Frölich[10] claimed that the excitability of the sympathetic nervous system is markedly increased by diminishing the calcium content of the blood. Reid[11] suggested the hypothesis that a reduction of the calcium in the body removes or weakens the inhibitory influence of the vagus, and thus results in hypertension.

That there is an interdependence between stimulation of the autonomic nervous system and changes in the potassium-calcium equilibrium of the blood has been shown by several investigators. Kraus and Zondek[12] showed that stimulation of the vagus increased the potassium in

7. Westphal, K.: Untersuchungen zur Frage der Entstehungsbedingungen des genuinen arteriellen Hochdruckes, Ztschr. f. klin. Med. **101**:559 and 584, 1925.

8. Mathison, G. C.: The Effects of Potassium Salts upon the Circulation and Their Action on Plain Muscle, J. Physiol. **42**:471, 1911.

9. Harrison, T. R.; Pilcher, C., and Wilson, C. P.: The Effects of Calcium, Barium and Potassium on the Cardiac Output of Normal Dogs, J. Pharmacol. & Exper. Therap. **32**:55, 1928.

10. Chiari, R., and Frölich, A.: Zur Frage der Nervenerregbarkeit bei der Oxalatvergiftung, Arch. f. exper. Path. u. Pharmakol. **66**:110, 1911.

11. Reid, W. D.: Arterial Hypertension, Boston M. & S. J. **192**:883, 1925.

12. Kraus, F., and Zondek, S. G.: Zur Lehre vom Aktionsstrom, Deutsche med. Wchnschr. **47**:1513, 1921.

the tissues, giving rise to a local acidosis. The reverse holds true on stimulation of the sympathetic nerves. Wollheim [13] and Benatt and Händel,[14] working on hydrogen-hydroxyl equilibrium, contended that a preponderance of calcium increased the removal of the hydroxl ion. Wollheim [13] and Berg, Hess and Sherman [15] observed that the cutting of the splanchnic nerve resulted in a fall in serum calcium, and that the cutting of the vagi resulted in a rise in calcium. Further recent work indicates not only that the sympathetic-parasympathetic balance determines the calcium-potassium ratio and thus the tissue reaction, but also that a change in this ratio may reverse the functional effect of nervous impulse on the innervated organ. Thus Kraus [16] and Zondek [17] demonstrated that if the calcium level is high, stimulation of the vagus augments rather than inhibits the action of the heart. Other investigators have shown that the action of the sympathetic nerves on the heart (Kohn and Pick [18]) and on the uterus (Turolt [19]) can be reversed. Finally, evidence is available (Konschegg,[20] Loewi,[21] Zondek,[22] Dressel and Jacobvitz,[23] Zondek and Reiter,[24] Baráth,[25] Zondek and Ucko,[26]

13. Wollheim, E.: Vegetatives Nervensystem und Elektrolytverteilung, Biochem. Ztschr. **151**:416, 1924.

14. Benatt, A., and Händel, M.: Kalium- und Calcium Wirkung auf die Harnacidität, Klin. Wchnschr. **3**:1621, 1924.

15. Berg, B. N.; Hess, A. F., and Sherman, E.: Changes in the Percentage of Calcium and Phosphorus of the Blood Following Section of the Sympathetic and Vagus Nerves, J. Exper. Med. **47**:105, 1928.

16. Kraus, F.: Ueber die Wirkung des Kalziums auf den Kreislauf, Deutsche med. Wchnschr. **46**:201, 1920.

17. Zondek, S. G.: Ueber die Bedeutung der Calcium- und Kalium-Ionen bei Giftwirkungen am Herzen, Arch. f. exper. Path. u. Pharmakol. **87**:342, 1920.

18. Kohn, R., and Pick, E. P.: Ueber Aenderung der Adrenalinwirkung nach Erregung der vagalen Endapparate, Arch. f. d. ges. Physiol. **184**:79, 1920.

19. Turolt, M.: Umkehr der Adrenalinwirkung auf den überlebenden Uterus, Arch. f. Gynäk. **115**:600, 1922.

20. Konschegg, A.: Ueber Beziehungen zwischen Herzmittel- und physiologischer Kationenwirkung, Arch. f. exper. Path. u. Pharmakol. **71**:251, 1913.

21. Loewi, O.: Ueber den Zusammenhang zwischen Digitalis- und Kalziumwirkung, Arch. f. exper. Path. u. Pharmakol. **82**:131, 1917.

22. Zondek, S. G.: Arch. f. exper. Path. u. Pharmakol. **88**:158, 1920; footnote 17.

23. Dressel, K., and Jacobovitz, M.: Untersuchungen über die theoretischen Grundlagen und die Indikationen der Calciumtherapie, Klin. Wchnschr. **1**:721, 1922.

24. Zondek, H., and Reiter, T.: Ueber das Wesen der Hormonwirkung, Ztschr. f. klin. Med. **99**:139, 1924.

25. Baráth, E.: Kalziumwirkung und Blutzucker, Med. Klin. **2**:1372, 1924.

26. Zondek, H., and Ucko, H.: Die Zweiphasenwirkung der Hormone, Klin. Wchnschr. **4**:6, 1925.

Kylin and Engel,[27] Zondek,[28] Kylin,[29] Zondek and Bernhardt,[30] Kylin [31]) that the effect of many drugs and hormones can be increased or reversed through changes in the local potassium-calcium equilibrium.

Since experimental observations suggest that changes in sympathetic-parasympathetic and potassium-calcium balance can be detected by their effect on the action of hormone, Kylin [5] investigated the relation between the reaction to epinephrine and the potassium-calcium ratio. He observed that in practically all cases with a potassium-calcium ratio of from 1.7 to 2.15, which is within his normal range, there were normal reactions to epinephrine. The blood pressure curve of patients with essential hypertension having a quotient over 2.15 was consistently vagotonic; that is, the patients exhibited a drop in blood pressure after an injection of epinephrine. Dressel and Jacobovitz [23] corroborated this work. In order to reestablish the potassium-calcium ratio and through it the normal sympathetic-parasympathetic balance, Kylin,[32] in 1924, treated patients with essential hypertension with calcium-atropine and observed a drop in the blood pressure and a change in the reaction to epinephrine from vagotonic to sympatheticotonic. Following these observations, series of analyses were made by different investigators on normal persons and patients with hypertension or other cardiovascular diseases, to determine the significance of these inorganic elements in the blood stream. Kylin,[5] Brems [33] and Loewenstein [34] found a definite rise in potassium content from the normal level in cases of essential hypertension, while the calcium values were either at or below the

27. Kylin, E., and Engel, A.: Ueber die Einwirkung der K-Ionen auf den Blutzuckerspiegel, Klin. Wchnschr. **4**:653, 1925.

28. Zondek, S. G.: Die Identität von Nerv-Ionen und Giftwirkung, Klin. Wchnschr. **4**:809, 1925.

29. Kylin, E.: Von der Bedeutung der K-Ionen für die Insulinwirkung, Klin. Wchnschr. **4**:1455, 1925.

30. Zondek, H., and Bernhardt, H.: Ueber die Beeinflüssbarkeit der Hypophysenhinterlappenextrakte, Ztschr. f. klin. Med. **101**:312, 1925.

31. Kylin, E.: Ueber den Einfluss der Ca- und K- Ionen auf die Insulinwirkung, Med. Klin. **21**:1262, 1925; Ueber die Bedeutung der Elektrolyten für die Hormonwirkung, ibid., p. 1580; footnote 5.

32. Kylin, E.: Ueber den Blutkalkspiegel bei der essentiellen Hypertonie, Zentralbl. f. inn. Med. **45**:471, 1924.

33. Brems, A.: Ueber den Kalium- und Calcium-Gehalt des Blutserums unter normalen und unter gewissen pathologischen Verhältnissen, Acta med. Scandinav. **66**:473, 1927.

34. Loewenstein, W.: Chemische Blutbefunde bei der essentiellen Hypertension und ihre Bewertung, Ztschr. f. klin. Med. **107**:52, 1928.

normal lower limits. In a series of cases, Kisch [35] observed a marked increase in potassium in patients with decompensated cardiac failure and an approximately normal amount in patients with compensated cardiac disease, regardless of the etiology and the level of the blood pressure. Spiro,[6] from a study of fifty-seven cases of vascular disorder, found that in patients with compensated circulation the potassium level was roughly within normal limits, both in the blood serum and in the corpuscles, although it tended toward the upper normal limits. In patients with circulatory and renal failure, there was a distinct rise in the potassium of the corpuscles which paralleled the rise in serum potassium. Since the flow of potassium from the corpuscles to the serum was less in persons with hypertension than in normal persons, Spiro concluded that the corpuscles acted as reservoirs, withdrawing and immobilizing the potassium as its level rose in the serum. Moreover, he observed that the calcium level had a tendency to be low.

Jansen [36] found a definite hypocalcemia in cardiac failure due to syphilis, nephrosclerosis and arterial hypertension. In patients with arterial hypertension, with or without renal involvement but without cardiac failure, the calcium values were at the lower level of the normal range. Anderson,[37] however, in sixteen cases of hypertension, observed normal calcium values as did Brems [33] in sixteen cases. Brems, moreover, found no connection between the potassium-calcium ratio and the reaction to epinephrine. Stieglitz [38] investigated forty-seven cases of pregnancy, with arterial hypertension as a secondary complication. Forty cases, which included those of nonpregnant and pregnant women without hypertension, were observed as controls. He found that the average calcium value in his pregnant patients coincided with that in his controls, and therefore he concluded that hypocalcemia is not a factor in the hypertension of pregnancy.

Although the experimental and clinical observations do not reveal any undisputed relationships between the calcium content of the blood serum and arterial hypertension, nevertheless it is claimed that the ele-

35. Kisch, F.: Der Kalium- und Calcium-Gehalt des Gesamtblutes Kreislaufkranker und das Verhalten desselben unter dem Einfluss körperlicher Arbeit. Klin. Wchnschr. **5**:1555, 1926.

36. Jansen, W. H.: Der Kalkgehalt des menschlichen Blutes unter pathologischen Berhältnissen, Deutsches Arch. f. klin. Med. **144**:14, 1924.

37. Anderson, W. T.: Meddelende fra Tursens medisiniske Lyseininstitut. Hospitalstid. **68**:1177, 1925.

38. Stieglitz, E. J.: Hypertension in Pregnancy, Arch. Int. Med. **39**:465 (April) 1927.

vation of blood calcium results in a fall of the blood pressure in arterial hypertension. Addison [39] claimed that the daily ingestion of from 4 to 12 Gm. of calcium chloride for four weeks resulted in a drop in the blood pressure. In 1930, Secher [40] stated that the intramuscular injection of parathyroid extract caused a simultaneous rise in the blood calcium and a drop in the blood pressure. He claimed that hypertension is due to an insufficient functioning of the parathyroid gland, and asserted that specimens of parathyroid obtained at autopsy from patients who had had hypertension show characteristic atrophy of the hormone-producing cells.

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON THE CHOLESTEROL LEVEL AND ITS RELATION TO ARTERIAL BLOOD PRESSURE

Westphal,[7] on feeding rabbits on a high cholesterol diet, observed that their blood pressure rose with an increase in the serum cholesterol. This increase in the blood pressure, he maintained, was independent of a disturbance of vasomotor function or internal secretion, and was due to the sensitizing effect of cholesterol on the muscle walls of the vessels. He expressed the belief that the sensitized muscular elements of the vessels then responded with increased contraction to substances in the blood serum. The experimental observations of Westphal have been supported also by the observations of Schmidtmann [41] and Fahr.[42] Schönheimer [43] and Shapiro,[44] however, found no relationship between the cholesterol level of the blood and high blood pressure. Furthermore, experiments involving injection of cholesterol into the blood stream have given contradictory results. Thomas,[45] in 1926, observed a rise in the blood pressure in four rabbits after injections of cholesterol.

39. Addison, W. L. T.: The Use of Calcium Chloride in Arterial Hypertension, Canad. M. A. J. **14**:1059, 1924.

40. Secher, K.: Eine Untersuchung über die Ursachen der Hypertonie, Acta med. Scandinav. **73**:309, 1930.

41. Schmidtmann, M.: Experimentelle Studien zur Pathogenese der Arteriosklerose, Virchows Arch. f. path. Anat. **237**:1, 1922.

42. Fahr, T.: Beiträge zur experimentellen Atherosklerose unter besonderer Berücksichtigung der Frage nach dem Zusammenhang zwischen Nebenierenveränderungen und Atherosclerose, Verhandl. d. deutsch. path. Gesellsch. **12**:125, 1922.

43. Schönheimer, R.: Ueber die experimentelle Cholesterinkrankheit der Kaninchen, Virchows Arch. f. path. Anat. **249**:1, 1924.

44. Shapiro, S.: Studies in Atherosclerosis: The Relation of Glands of Internal Secretion to Its Development, M. J. & Rec. **126**:284, 1927.

45. Thomas, E.: Recherches expérimentales touchant l'influence de la cholestérine sur le développement de l'hypertension artérielle, Arch. d. mal. du coeur **19**:641, 1926.

Thölldte [46] was unable to verify the experimental observations of Westphal [7] and Schmidtmann.[41]

Westphall,[7] investigating a series of eighty cases of essential hypertension, found that the cholesterol level was above the normal range in 71 per cent of the cases. Weil and Guillaumin [47] found high cholesterol values in the plasma of patients with hypertension. Askanazy [48] observed a hypercholesteremia in most of his cases of hypertension. Thus, on the basis of observations on man and experiments on animals, Westphal and others considered that cholesterol is one factor in the genesis of essential hypertension.

However, Mjassnikow [49] claimed that hypercholesteremia was present in less than 50 per cent of his cases in which atherosclerosis was only weakly developed. Loewenstein [34] reported only one case of hypercholesteremia among fifty cases of hypertension investigated. Harris and Lipkin [50] also found normal cholesterol values in ten of eleven patients with hypertension. Moreover, intramuscular injections of cholesterol that raised the cholesterol level of the serum markedly in four cases of hypertension were unassociated with any changes in blood pressure.

THE PROBLEM

With the elimination of the two supposed constrictor substances in the circulating blood, guanidine and amino-acids, as etiologic agents in the development of the increased peripheral resistance in arterial hypertension, the claims of the proponents of the potassium, calcium and cholesterol hypotheses have gained significance. A definite confirmation of these hypotheses by direct observations would also offer a rational therapeutic approach to arterial hypertension. Since the observations quoted by previous investigators in this field are open to dispute, both because of the faulty and inaccurate methods used and because of insufficient information concerning the clinical condition of the patients, this investigation was undertaken to determine whether or not changes can be demonstrated in the level of the potassium, calcium

46. Thölldte, M.: Hypercholesterinämie, Blutdruck und Gefässveränderungen im Tierversuch, Beitr. z. path. Anat. u. z. allg. Path. **77**:61, 1927.

47. Weil, M. P., and Guillaumin, C. O.: Hyperglycémie, hypercholestérinémie augmentation des composés uriques globulaires et hypertension artérielle variable, son origine rénale, Ann. de méd. **19**:415, 1926.

48. Askanazy: Hypertonie und Hypercholesterinämie, München med. Wchnschr. **74**:1793, 1927.

49. Mjassnikow, G. L.: Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, Ztschr. f. klin. Med. **102**:65, 1926.

50. Harris, I., and Lipkin, I. J.: High Blood Pressure and Cholesterin, Brit. M. J. **1**:587, 1930.

and cholesterol of the blood when tested by the reliable methods available and when the patients are selected after a detailed investigation of the clinical state. Moreover, since the calcium level of the blood varies inversely with the inorganic phosphate level, all other things being equal (Binger,[51] Salvesen and Linder,[52] Peters and Eiserson [53]), an increase in the average inorganic phosphate level would corroborate any evidence of a decrease in the average calcium level. Hence, the better to control the observations on calcium indirectly, determinations of the inorganic phosphate level were also performed. Finally, if changes actually take place in the potassium-calcium ratio in arterial hypertension, it would be significant to ascertain whether such a change is associated with an alteration in the cholesterol level.

METHODS

The chemical methods used have been devised recently and, with the exception of the cholesterol method, gave satisfactory results throughout the course of the investigations.

Potassium was determined by the method developed by Taylor.[54] Duplicate analyses by this method gave results which agreed within 2 per cent. One minor change was adopted in this procedure. It was found that a gel of anhydrous tungstic acid formed when the standard solutions were evaporated to dryness. To obviate this difficulty, the standard solutions were evaporated only to 2 cc. Satisfactory precipitation of potassium was then obtained by the addition of 2 cc. of sodium cobaltinitrite and 2 cc. of 95 per cent alcohol.

The method for the determination of calcium that was developed by Fiske and Logan [55] offered no difficulties. At the suggestion of Taylor,[56] the following changes were made in this procedure for convenience and speed: 1. The precipitation of the calcium was completed in one and one-half hours instead of in twelve. Results obtained by using this modification checked within 1 per cent of those obtained

51. Binger, C.: Toxicity of Phosphates in Relation to Blood Calcium and Tetany, J. Pharmacol. & Exper. Therap. **10**:105, 1917.

52. Salvesen, H. A., and Linder, G. C.: Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, J. Biol. Chem. **58**:617, 1923.

53. Peters, J. P., and Eiserson, L.: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155, 1929.

54. Taylor, F. H. L.: The Determination of Potassium in Blood Serum, J. Biol. Chem. **87**:27, 1930.

55. Fiske, C. H., and Logan, M. A.: To be published, J. Biol. Chem.

56. Taylor, F. H. L.: Personal communications to the authors.

from precipitations obtained over a period of twelve hours. 2. The fifteen-thousandths normal hydrochloric acid was replaced by hundredth normal acid. Two cubic centimeters of the hundredth normal acid was added to the ignited calcium oxide instead of 1 cc. of the fifteen-thousandths normal acid, and titrated by hundredth normal sodium hydroxide.

The method of Fiske and Subbarrow [57] was used for the determination of inorganic phosphorus, and it was quite satisfactory. The method for the saponification of cholesterol of Bloor, Pelkan and Allen [58] was accurate within only from 7 to 10 per cent.

RESULTS

Seventy-five cases of hypertension, twenty-four in males and fifty-one in females, between the ages of 19 and 75 years, were studied. Twenty-nine of these cases exhibited clinical evidence of cardiac failure, six showed clinical evidence of renal involvement and three exhibited both cardiac and renal involvement so far as could be ascertained by clinical and laboratory studies. Of the seventy-five cases, forty-five showed clinical evidence of arteriosclerosis. All patients were in the hospital for at least one week previous to the tests. Blood samples were obtained in the postabsorptive state at 8 a. m. from the cubital vein and were analyzed immediately. Measurements of the blood pressure were obtained with the patient in the horizontal position. The systolic pressure ranged between 155 and 270 mm. of mercury, the diastolic between 70 and 160 mm.; the average systolic pressure was 189 mm.; the average diastolic, 105 mm.

Table 1 presents the potassium, calcium, cholesterol and inorganic phosphorus content of the blood serum as well as the potassium-calcium and calcium-phosphorus ratios in seventy-five cases of hypertension with and without secondary complications. Table 2 presents the results of similar measurements in twenty-five control cases without hypertension. The values presented in table 2 compare favorably with those reported recently by other authors using the same methods.

The calcium in the Fiske-Logan method was about 0.6 mg. per hundred cubic centimeters of serum less than that reported by authors using the Kramer-Tisdall or Jansen methods, for three reasons: 1. The former methods involved the oxidation of the calcium

57. Fiske, C. H., and Subbarow, Y.: Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

58. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**: 191, 1922.

TABLE I.—*The Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium and Calcium-Phosphorus Ratios of the Blood Serum in Seventy-Five Cases of Arterial Hypertension*

Case	Age	Sex	Arterial Blood Pressure: Systolic, Mm. Mercury	Arterial Blood Pressure: Diastolic, Mm. Mercury	Pulse Pressure, Mm. Mercury	Cardiac (C) or Renal (R) Impairment	Potassium, Mg.	Calcium, Mg.	Cholesterol, Mg.	Phosphorus, Mg.	Potassium-Calcium Ratio	Calcium-Phosphorus Ratio
1	67	M	160	80	80	C.	23.30	8.80	165.5	3.62	3.32	2.43
2	..	F	170	75	95	..	23.98	8.77	164.5	3.85	2.73	2.28
3	55	F	180	90	90	C.	23.15	9.77	153.4	3.81	2.37	2.56
4	66	F	195	120	75	C.	24.00	9.60	160.1	4.30	2.50	2.23
5	69	F	195	115	80	..	20.00	11.50	166.6	4.60	1.74	2.50
6	75	F	175	105	70	C.	23.51	9.92	174.6	4.73	2.37	2.10
7	75	F	210	100	100	..	20.40	9.97	122.4	3.42	2.05	2.92
8	60	F	155	110	45	..	24.84	9.58	297.4	4.97	2.59	1.93
9	..	F	216	120	96	..	21.20	10.26	271.8	4.13	2.05	2.48
10	40	M	180	100	80	C.	25.31	9.20	167.7	4.30	2.75	2.14
11	..	M	185	140	55	C.	22.47	9.80	223.2	4.73	2.29	2.07
12	..	M	180	110	70	C.	20.00	9.99	208.8	3.86	2.02	2.59
13	19	M	165	75	90	C.	24.70	9.10	182.9	5.10	2.71	1.78
14	62	F	235	125	110	..	20.30	9.92	196.8	4.06	2.00	1.94
15	62	F	220	120	100	R.	21.73	9.40	260.3	4.21	2.31	2.23
16	64	F	242	120	122	C. R.	26.20	9.38	206.5	4.32	2.79	2.17
17	72	F	170	130	40	C.	21.51	10.72	227.2	4.00	2.01	2.68
18	40	M	170	95	75	..	22.53	9.61	201.0	4.20	2.35	2.09
19	72	F	265	100	95	C. R.	25.00	10.06	240.2	4.20	2.49	1.90
20	72	F	190	100	90	C.	23.52	10.20	156.3	3.20	2.31	3.18
21	61	F	180	95	85	R.	20.00	9.67	247.4	3.60	2.07	2.69
22	19	F	160	80	80	..	20.15	9.60	134.6	3.00	2.10	3.20
23	69	F	210	100	110	C.	19.60	8.00	208.3	3.36	2.45	3.00
24	64	F	185	100	85	C.	22.86	11.60	223.2	2.95	1.97	3.98
25	60	F	186	110	76	C.	21.39	9.54	195.8	4.00	2.29	2.38
26	..	F	198	100	98	C.	21.05	9.05	181.1	3.26	2.33	2.78
27	60	F	180	90	90	C.	22.22	9.60	211.9	5.59	2.32	1.72
28	68	F	230	120	110	C.	18.69	9.60	183.8	3.85	1.95	2.49
29	67	M	200	100	100	..	18.27	9.70	219.3	3.13	1.88	3.10
30	45	F	170	90	80	..	23.53	10.30	250.0	4.70	2.29	2.19
31	42	F	170	110	60	R.	24.24	9.60	223.2	6.06	2.51	1.58
32	68	M	170	70	100	C.	23.30	10.24	210.1	2.68	2.28	3.82
33	50	M	175	120	55	R.	21.62	10.80	192.5	3.98	2.00	2.71
34	47	M	195	120	75	C. R.	17.86	10.12	288.0	3.94	1.77	2.57
35	30	F	230	144	86	R.	22.86	9.50	231.5	6.84	2.41	1.39
36	73	F	170	90	80	..	20.83	10.70	347.2	4.30	1.95	2.49
37	74	F	190	125	65	C.	20.00	9.20	187.9	2.33	2.17	2.71
38	..	F	180	110	70	..	20.10	9.20	221.2	3.56	2.14	2.64
39	60	F	160	80	80	..	21.62	9.40	168.9	3.92	2.30	2.39
40	60	F	175	78	97	..	20.83	10.69	147.9	4.68	1.95	2.29
41	68	F	176	112	64	C.	20.83	10.17	177.3	4.02	2.05	2.53
42	66	F	162	74	88	..	21.74	10.19	233.6	4.10	2.14	2.48
43	52	F	225	125	100	..	18.71	10.19	191.7	4.00	1.84	2.55
44	51	F	160	100	60	..	19.40	10.77	238.0	3.33	1.76	3.25
45	75	M	170	100	70	..	19.31	9.36	170.1	3.32	2.06	2.74
46	58	M	180	110	70	..	25.01	9.56	225.2	3.81	2.59	2.54
47	77	M	160	95	65	C.	21.02	9.67	169.6	2.94	2.18	3.29
48	73	M	160	100	60	C.	22.34	8.97	195.3	2.74	2.49	3.27
49	73	F	220	90	130	..	22.27	9.17	174.8	3.38	2.53	2.71
50	65	F	170	86	84	..	23.56	11.23	251.8	4.38	2.10	2.57
51	50	F	254	134	120	C.	24.09	10.08	155.3	4.44	2.39	2.27
52	21	F	145	80	65	..	19.31	10.08	168.3	4.09	1.92	2.46
53	62	F	208	124	84	..	20.42	10.28	201.6	4.44	1.99	2.31
54	38	M	148	110	38	R.	19.23	8.65	203.5	3.57	2.28	2.42
55	56	M	184	120	64	C.	20.60	8.78	156.1	3.83	2.35	2.29
56	44	M	220	150	70	..	22.99	9.23	208.3	4.47	2.49	2.06
57	47	M	190	110	80	..	17.39	9.43	245.1	4.37	1.84	2.16
58	40	F	160	90	70	..	19.14	9.43	219.5	4.76	2.03	1.98
59	47	F	170	120	50	..	22.86	9.21	192.3	5.63	2.48	1.64
60	59	F	215	130	85	..	22.73	9.97	185.2	4.21	2.28	2.37
61	60	F	165	98	67	C.	24.24	9.97	192.3	4.68	2.49	2.13
62	52	F	200	110	90	..	21.98	9.43	200.0	3.90	2.33	2.42
63	43	F	150	70	80	C.	26.63	9.11	138.8	4.21	2.92	2.16
64	65	F	210	86	124	C.	21.74	9.65	183.5	3.85	2.25	2.18
65	53	M	260	160	100	C.	23.12	9.61	225.2	3.90	2.41	2.46
66	46	F	230	140	90	..	22.86	9.78	294.2	4.20	2.33	2.33
67	64	M	190	90	100	..	23.33	9.83	171.2	3.72	2.37	2.64
68	32	M	145	90	55	..	23.53	10.53	208.3	4.13	2.24	2.55
69	58	M	190	70	120	C.	21.85	9.32	174.2	4.63	2.35	2.01
70	74	F	270	130	140	..	23.26	9.76	226.2	4.94	2.38	1.98
71	56	F	205	105	100	..	23.95	9.16	227.3	3.49	2.63	2.61
72	47	M	212	118	94	..	22.99	10.43	148.8	4.65	2.20	2.24
73	60	M	200	95	105	..	22.60	9.55	166.7	4.38	2.37	2.18
74	60	F	220	110	110	C.	26.66	9.17	271.7	4.00	2.91	2.29
75	69	F	195	75	120	..	24.24	9.95	255.1	5.26	2.44	1.89
Average							22.15	9.75	204.5	4.09	2.28	2.43

oxalate precipitate by dilute potassium permanganate. Any organic material brought down by the precipitate would obviously increase the final calcium value. 2. Unless the p_H of the solution is carefully con-

TABLE 2.—*The Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium and Calcium-Phosphorus Ratios of the Blood Serum in Twenty-Five Control Cases*

Case	Age	Sex	Arterial Blood Pressure: Systolic, Mm. Mercury	Arterial Blood Pressure: Diastolic, Mm. Mercury	Arterial Blood Pressure: Pulse Pressure, Mm. Mercury	Diagnosis and Comments	Potassium, Mg.	Calcium, Mg.	Cholesterol, Mg.	Phosphorus, Mg.	Potassium-Calcium Ratio	Calcium-Phosphorus Ratio
1	50	F	126	85	41	Cinchona bark poisoning	19.80	10.62	192.3	4.42	1.86	2.40
2	65	F	120	60	60	Gastro-enteritis	18.18	9.40	161.3	3.05	1.93	3.01
3	65	M	110	50	60	Lymphoblastoma	20.40	9.90	161.3	3.68	2.06	2.72
4	65	F	130	84	46	Cancer of stomach ?	17.17	10.90	126.2	4.68	1.58	2.33
5	46	F	142	84	56	Frontal sinusitis	20.20	10.50	162.3	4.04	1.93	2.60
6	52	F	135	85	50	Myxedema; secondary anemia	19.01	9.80	131.6	4.94	2.02	1.98
7	60	M	138	70	68	Gout; infectious arthritis; arteriosclerosis	20.20	9.37	120.6	4.06	2.16	2.31
8	75	M	145	80	65	Chronic constipation	18.50	9.51	206.5	3.42	1.96	2.78
9	49	M	135	70	65	Diabetes mellitus; tabes dorsalis	19.90	9.60	.....	3.39	2.07	2.83
10	62	M	125	75	50	Lobar pneumonia; mild arteriosclerosis	20.00	9.32	151.2	4.09	2.15	2.28
11	68	F	125	80	45	Ulcer or cancer of stomach; arteriosclerosis	20.83	9.65	250.0	4.76	2.16	2.03
12	49	M	135	90	45	Bronchopneumonia	18.90	10.00	165.5	3.04	1.89	3.29
13	60	F	135	85	50	Cancer of stomach	21.05	9.43	189.2	5.23	2.23	1.80
14	65	M	130	65	65	Pleurisy; arteriosclerosis	21.97	9.44	208.3	4.71	2.33	2.00
15	69	F	125	60	65	Lobar pneumonia; generalized arteriosclerosis	21.51	9.40	271.7	4.97	2.29	1.89
16	55	F	110	60	50	Diabetes; arteriosclerosis	20.20	10.69	195.3	4.23	1.89	2.53
17	40	M	130	95	35	Tumor of the brain or subarachnoid hemorrhage	21.00	9.80	137.3	4.14	2.14	2.48
18	55	F	125	58	67	Bronchopneumonia	18.60	10.03	142.9	3.76	1.86	2.67
19	78	F	125	50	75	Cancer of cecum; secondary anemia	18.18	8.80	133.0	4.71	2.07	1.87
20	60	M	135	80	55	Arteriosclerosis; tertiary syphilis	21.62	9.30	204.9	4.82	2.32	1.93
21	42	M	125	80	45	Alcoholic neuritis; "Jamaica ginger" paralysis	18.02	9.65	195.3	4.79	1.87	2.01
22	40	M	130	80	50	Neuritis and obesity	21.50	9.54	164.2	4.01	2.25	2.38
23	59	M	135	85	50	Pleurisy	21.27	10.12	260.3	4.97	2.10	2.04
24	42	F	130	90	40	Pleurisy	23.53	9.73	195.3	5.40	2.42	1.80
25	54	F	140	90	50	Peptic ulcer	18.18	10.23	162.3	4.30	1.78	2.38
Average							19.99	9.79	171.6	4.30	2.05	2.33

trolled, magnesium oxalate is also precipitated. 3. Since the calcium is precipitated by the oxalate ion, the incomplete removal of the precipitating medium would again raise the calcium value. These sources of error are eliminated in the Fiske-Logan method by the precipitation of the normal blood serum which has a p_H of about 7.4, and by igniting

the calcium oxalate precipitate to remove organic material and the excess oxalate ion.

Table 3 contains a comparison of the range and average values of potassium, calcium, cholesterol and inorganic phosphorus in the serum in cases in which there was hypertension and in cases in which hypertension was not present. The cases with hypertension have been subdivided into three groups: (1) cases of uncomplicated hypertension;

TABLE 3.—*The Average and Maximal Variations of the Potassium, Calcium, Cholesterol and Inorganic Phosphorus Content and the Potassium-Calcium Ratio and Calcium-Phosphorus Ratio of the Blood Serum in Seventy-Five Cases with Hypertension and in Twenty-Five Control Cases* *

	Number of Cases	Potassium		Calcium		Cholesterol	
		Range	Average	Range	Average	Range	Average
Control	25	17.2-23.5	20.00	8.8-10.9	9.80	120.6-260.3	171.6
Essential hypertension	37	17.4-25.0	21.68	9.2-11.5	9.88	134.0-297.4	212.7
Hypertension with renal impairment	9	17.9-26.2	22.10	8.6-10.8	9.68	192.5-260.3	227.0
Hypertension with cardiac impairment	32	18.7-29.2	22.80	8.0-10.7	9.62	138.8-271.7	194.0
Hypertension with and without complications	75	17.4-29.2	22.15	8.0-11.5	9.75	134.0-297.4	204.5

	Number of Cases	Phosphorus		Potassium-Calcium Ratio		Calcium-Phosphorus Ratio	
		Range	Average	Range	Average	Range	Average
Control	25	3.0-5.4	4.3	1.78-2.42	2.05	1.8-3.0	2.33
Essential hypertension	37	3.0-5.6	4.1	1.74-2.63	2.19	1.6-3.2	2.41
Hypertension with renal impairment	9	3.6-6.8	4.5	1.77-2.79	2.29	1.6-2.7	2.18
Hypertension with cardiac impairment	32	2.3-5.6	3.9	1.77-3.32	2.38	1.7-3.9	2.50
Hypertension with and without complications	75	2.3-6.8	4.1	1.74-3.32	2.32	1.6-3.9	2.43

* All values are expressed in milligrams per hundred cubic centimeters of blood serum.

(2) cases of hypertension with renal involvement; (3) cases of hypertension with cardiac failure. Table 3 shows that the average potassium level tends to increase from a level of 20 mg. per hundred cubic centimeters of serum in control cases, to 22.15 mg. per hundred cubic centimeters in cases of hypertension with and without involvements. When the cases were separated clinically into groups according to complications, those with cardiac involvement showed an average level of 22.8, mg., those with renal involvement, 22.1 mg., and the uncomplicated cases of hypertension, 21.68 mg. per hundred cubic centimeters of serum.

When the potassium level was charted against the systolic pressure (chart 1) the potassium value rose distinctly from 20 to 22 mg. per hundred cubic centimeters of serum, between the systolic range of from 150 to 180 mm. of mercury. From that point the rise seemed to be approaching a limit, for at a systolic pressure of 230, the potassium level

was only 22.5 mg. per hundred cubic centimeters of serum. A similar relation was found when the potassium values were charted against the diastolic pressure. This elevation of the potassium level with the blood pressure is largely due to the relatively high potassium values in patients with circulatory failure, as will be shown presently.

As indicated in chart 2, no change was observed in the calcium level. The average calcium level in twenty-five control cases was found to be 9.8 as compared with 9.75 mg. per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without complications. The latter group, when subdivided, showed a calcium level of

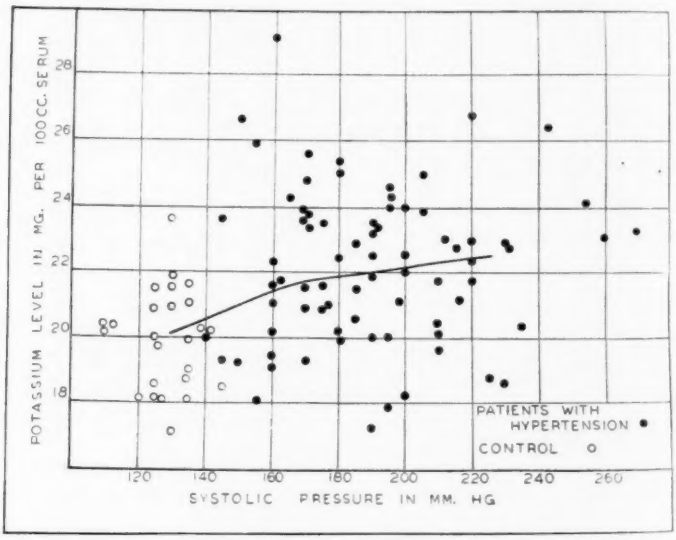

Chart 1.—The distribution of the potassium level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

9.88 mg. per hundred cubic centimeters of serum for uncomplicated cases of hypertension; 9.68 mg. for cases with renal involvement, and 9.62 mg. for cases with cardiac decompensation. Since the calcium method was accurate only within 1 per cent, the average calcium level of these groups was well within the limits of the observations on the controls. The observed range of calcium values for the control cases was from 8.8 to 10.9 mg. per hundred cubic centimeters of serum, or very similar to the range in the cases of uninvolved hypertension (9.2 to 11.5 mg. per hundred cubic centimeters). Moreover, when the calcium level of the hundred cases studied was plotted against the systolic or

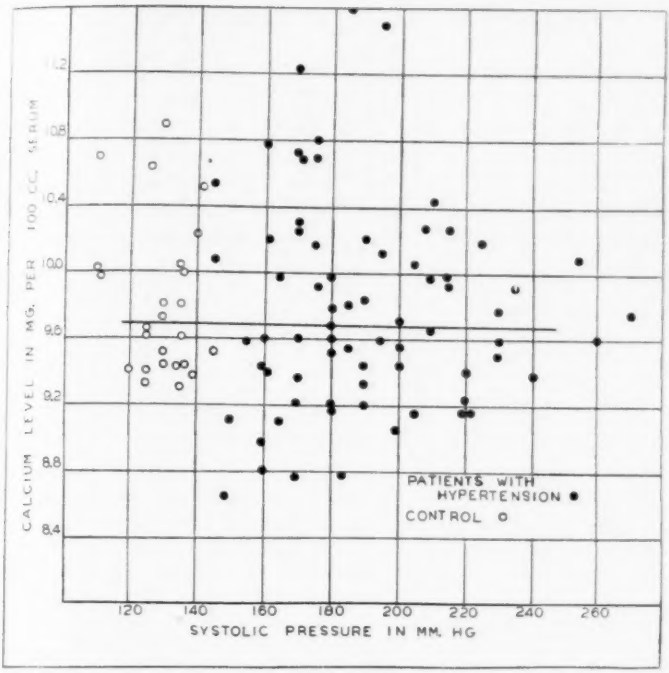

Chart 2.—The distribution of the calcium level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

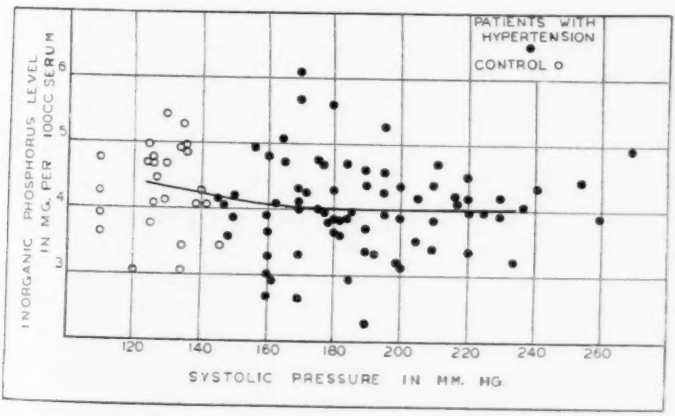

Chart 3.—The distribution of the inorganic phosphorus level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

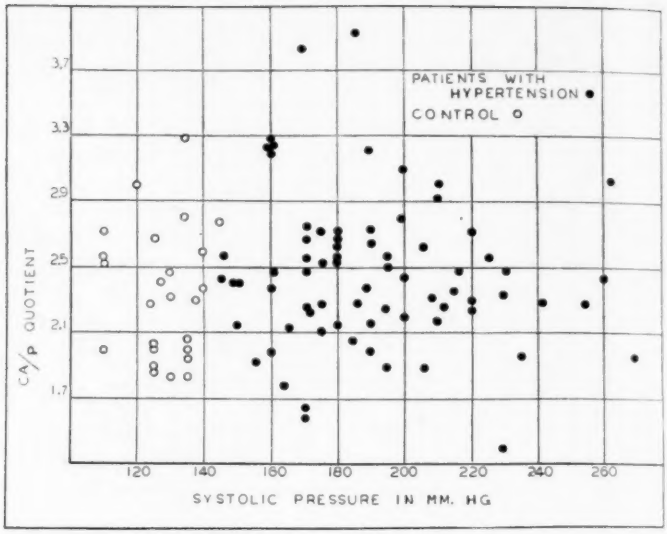

Chart 4.—The distribution of the values for the calcium-inorganic phosphorus ratio in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

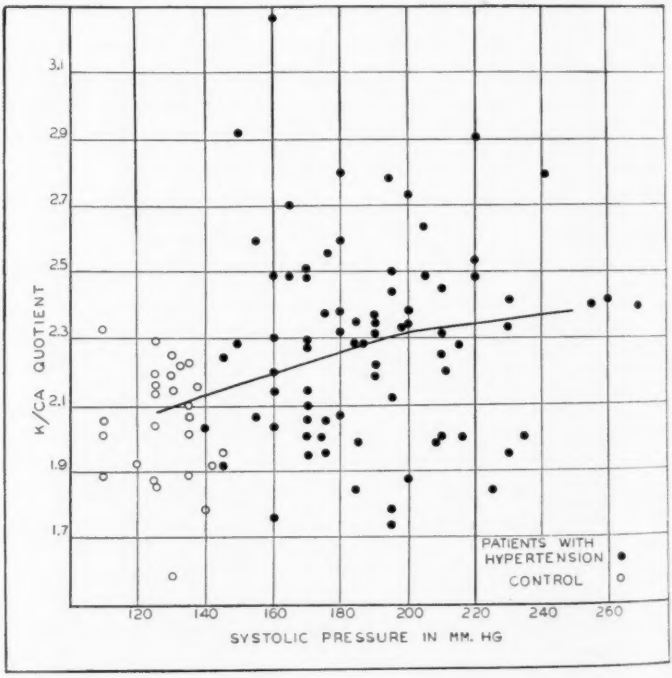

Chart 5.—The distribution of the values for the potassium-calcium ratio in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

diastolic blood pressure, the calcium level showed no tendency to rise as the blood pressure rose.

The observations on the inorganic phosphorus level corresponded to those on the calcium level, for the inorganic phosphorus level in seventy-five cases of mixed hypertension (4.1 mg. per hundred cubic centimeters), showed no tendency to increase, as one would expect if the calcium level were to decrease (chart 3). Also the calcium-inor-

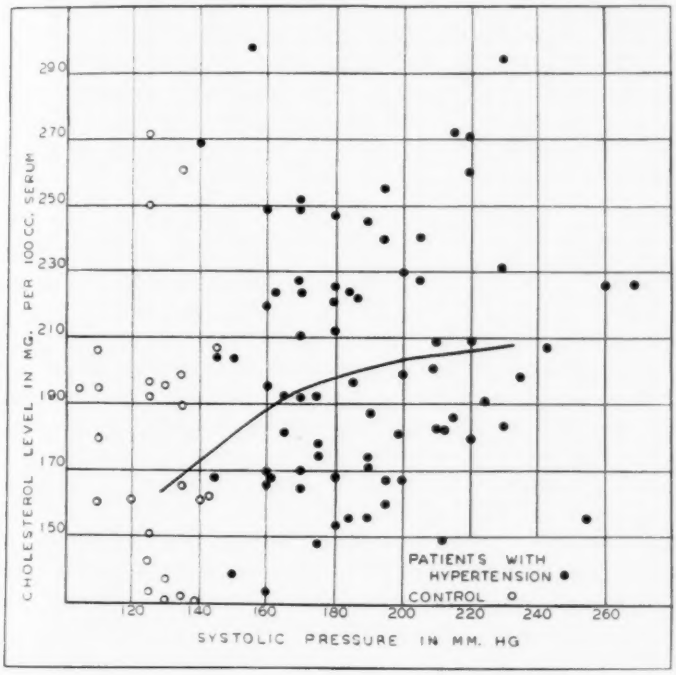

Chart 6.—The distribution of the cholesterol level in the blood serum and its relation to the height of the systolic blood pressure in seventy-five patients with hypertension and in twenty-five control cases.

ganic phosphorus ratios in the seventy-five cases of hypertension (2.4), showed no tendency to decrease. In hypertension with renal involvement, however, since renal dysfunction permits a greater retention of inorganic phosphorus, this ratio dropped to 2.18 (chart 4).

The values for the potassium-calcium ratio roughly followed the potassium values, for the quotient rose from 2.05 for the control group, to 2.32 for the entire group of patients with hypertension. Divided into groups, the ratio of the uninvolved group was 2.19; that of the group

with cardiac involvement was 2.38, and that of the group with renal involvement was 2.29. Plotted against the systolic or diastolic pressure, the potassium-calcium quotient showed the same type of curve as potassium. It rose from 2.1 at 140 mm. to 2.32 at 200 mm. of mercury (chart 5). The explanation of this will be discussed later.

The blood cholesterol also showed a rise in level from a control average of 171.6 to 204.5 mg. per hundred cubic centimeters of blood in cases of mixed hypertension. In nine cases of hypertension with renal involvement, the level rose to 227 mg., corresponding to previous observations on increase in blood cholesterol with renal dysfunctions.

Plotted against the systolic or diastolic pressure, the cholesterol rose from 170 mg. per hundred cubic centimeter of blood at 140 mm. to 200 mg. per hundred cubic centimeter of serum at 200 mm. of mercury (chart 6).

COMMENT

The observations indicate that the seventy-five cases of hypertension with or without secondary complication showed an average increase of 9 per cent in the potassium of the blood serum above the average level of the control group. Division of the cases of hypertension into groups shows that the cases without renal or cardiac involvement showed an average increase of 7.7 per cent as compared with an increase of 5.2 per cent in cases with renal involvement, and an increase of 12.2 per cent in cases of cardiac decompensation. The following are the most plausible interpretations for these differences: 1. Changes that take place in cardiovascular dysfunction affect the potassium metabolism of the body in such a way as to cause an increase in blood potassium. 2. Changes that take place in the parasympathetic-sympathetic balance so affect the potassium-calcium ratio that the blood pressure rises, and renal and cardiac failure develop as secondary involvements. 3. An overactivity of the parasympathetic nervous system occurs in a few instances, and this produces an increase in the blood potassium which in turn affects the arteriolar system or the blood pressure. The first of the foregoing inferences is probably correct, for in thirty-seven cases of uninvolved hypertension, normal potassium values were present in 78 per cent and high values in only 21 per cent; likewise, 65 per cent showed normal potassium-calcium values, and only 29 per cent, high values. If changes in this ratio are factors in the etiology of hypertension, it is difficult to explain why only eleven of the thirty-seven uncomplicated cases of hypertension (29 per cent) showed high quotients. If, however, these changes in potassium level and potassium-calcium quotient are indicative of altera-

tions in cardiorenal function, then it becomes plausible that 56 per cent of the cases of hypertension with renal involvement and 63 per cent of those with cardiac involvement showed abnormally high potassium-calcium quotients. Moreover, since the potassium-calcium ratio for the thirty-seven uncomplicated cases of hypertension was 2.19 (as compared with a value of 2.05 in the control cases) which is well within the normal range of from 1.78 to 2.35, and since this ratio was only correct within 6 parts in 200, it would be hazardous to say that this slight rise in the ratio led to hypertension or was indicative of a change in parasympathetic-sympathetic balance, which led to hypertension. Thus, the fact that patients with clinical evidence of hypertensive cardiac failure showed an elevation of the potassium level of the blood, supports the conception that the raised potassium level was the result and not the cause of arterial hypertension.

The eight cases of involved hypertension that showed high potassium values may indeed have had some degree of cardiac failure, because it is well recognized that the evaluation of the cardiac reserve in arterial hypertension often offers considerable difficulty. Frequently, when symptoms of cardiac failure are still absent, the cardiac reserve is already impaired. It is evident from clinical observations that "essential hypertension," "primary arterial hypertension," and "uncomplicated hypertension" are only relative terms and designate but one stage of the disease. A patient who suffers from uncomplicated hypertension may succumb later as a result of cardiac or renal insufficiency. It is therefore probable that several of the cases that did not exhibit clinical evidence of cardiac failure nevertheless had impaired circulatory function which resulted in a rise in the potassium of the serum. Finally, the observation of an elevated potassium content of the blood in cardiac failure without hypertension (Spiro [6] and Kisch [8]) is weighty evidence against the theory that an increase of potassium in the blood is the cause of arterial hypertension.

Elevation of the blood potassium without hypertension may be due to other causes than an overactivity of the parasympathetic nervous system. But even if one were to concede that in certain instances of uncomplicated hypertension the elevation of the blood potassium is an indication of an overactive parasympathetic system, there is no evidence that such increase of the blood potassium affects the arteriolar resistance and thus the arterial pressure. That, indeed, an elevated level in the blood potassium, as observed in the few cases of essential hypertension, does not increase the blood pressure is substantiated by the observataion that there is a high potassium level in the blood of patients with bronchial asthma, gastric ulcer and in certain types of neurosis.[59]

59. Kylin, E.: Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926, p. 86.

An analysis of the literature reveals that the claims that the parasympathetic part of the autonomic nervous system is overactive in arterial hypertension are based on impressions and assumptions rather than on careful analytic observations. There is a tendency to assume that an overactivity of the psychic function is associated with stimulation of the autonomic system; and it is often not appreciated that psychic overactivity and sympathetic overactivity frequently are not in causal relationship and are present alone and not in combination. Moreover, there may be an overactivity of one or more sections of the sympathetic or parasympathetic nervous system with normal functioning of the rest of the system. Dennig, Fischer and Beringer[60] observed that the responses of the vegetative nervous system do not depend essentially on the psychic state of the patient. Recently, Weiss and Patek[61] made a study of the psychic state and the autonomic nervous system in forty-two patients with arterial hypertension and in thirty-seven control cases. While the patients suffering from hypertension were overexcitable, impulsive and sensitive, the tests applied for the study of the autonomic nervous system failed to prove a definite overactivity of the parasympathetic nervous system.

It has been definitely established by the analyses presented that no change from the normal range occurs in the calcium level of patients with hypertension. The averages for the cases involved and uninvolved hypertension are well within the normal range and compare favorably with normal values obtained by other authors using the same method. That the calcium level of patients with hypertension does not change is indirectly verified by the fact that the inorganic phosphorus level and the calcium-inorganic phosphorus ratio are normal. These results remove any rational basis for the administration of calcium for the elevation of the blood calcium through potent extracts of the parathyroid glands as beneficial therapeutic procedures in arterial hypertension.

Of the thirty-seven patients with uncomplicated hypertension, 54 per cent presumably had hypercholesteremia, and 46 per cent showed normal values. When, however, the records of the patients with hypercholesteremia were examined, it was found that only five of the group had no recorded secondary complications other than hypertension; two patients were recovering from bronchial pneumonia; two suffered from duodenal ulcers; three from cerebral hemorrhages; three had a high nonprotein nitrogen content of the blood and low specific gravity of

60. Dennig, H.; Fischer, K., and Beringer, K.: Psyche und vegetatives Nervensystem, Deutsches Arch. f. klin. Med. **167**:26, 1930.

61. Weiss, S., and Patek, A. J., Jr.: Unpublished study.

the urine; one was passing through menopause; one had had an oophorectomy; one had tertiary syphilis, and two had cardiac asthma. It has been repeatedly observed [62] that the cholesterol level often sinks in infections (such as bronchopneumonia) and rises during recovery; that the level rises markedly in most forms of internal bleeding and in renal involvement, and that various changes in the cholesterol level occur in disturbances of the secretions of the gonads. Thus, of thirty-seven patients with uninvolved hypertension, only 13 per cent had a hypercholesteremia that could not be explained on the basis of known complications. Moreover, a too rigid interpretation of cholesterol values is rather hazardous. The cholesterol level in normal people is known to fluctuate as much as 35 mg. per hundred cubic centimeters during the course of a month (Muller [62]). Therefore, a marked deviation of the cholesterol level from the normal range, such as is reported in pernicious anemia and diabetes, must necessarily be present before any definite rôle can be attributed to the cholesterol content of the blood in arterial hypertension. Such an alteration has not been observed. It should be remembered also that although the usual functional tests of the kidneys fail to reveal an impaired renal function, a considerable encroachment on the normal reserve of the kidneys may be present in arterial hypertension. Observations by Weiss and Ellis [63] indicate that in essential hypertension the flow of blood through the kidneys, as measured with the urea clearance test, may be considerably reduced although the function of the kidney as measured by other methods is still normal. Thus the slightly elevated cholesterol level observed in a few instances may be the result of early renal involvement.

In attempting to correlate changes in the potassium-calcium ratio to changes in the cholesterol level, it was found that of the twenty presumable cases of hypercholesteremia observed in the patients with involved hypertension, only 25 per cent showed a ratio of over 2.35; of the five cases of hypercholesteremia with no known involvements affecting the cholesterol level, not one showed a high potassium-calcium ratio. Thus in these cases of hypertension, there is definitely no relation between changes in the potassium-calcium ratio and the cholesterol level.

The results of this study, therefore, do not support the hypothesis that increased potassium, increased cholesterol or decreased calcium content of the circulating blood alone or in combination is responsible for the increase in the arteriolar resistance of arterial hypertension. Since the claims that other circulating substances, such as guanidine, the amino-acids, epinephrine and chloride ions, cause arterial hypertension are similarly not supported by reliable, direct observations in man, one

62. Muller, G. L.: Personal communications to the authors.

63. Weiss, S., and Ellis, L. B.: Unpublished observations.

must conclude that direct experimental support is thus far lacking in the numerous clinical suggestions that a "circulating chemical element" is responsible for increased peripheral resistance, and therefore is the responsible factor in the causation of arterial hypertension.

SUMMARY AND CONCLUSIONS

1. A study of the significance of the potassium-calcium ratio and the inorganic phosphorus and cholesterol of the blood serum in seventy-five cases of hypertension and twenty-five control cases is presented.

2. The average potassium level rose from 20 to 22.15 mg. per hundred cubic centimeters of serum in seventy-five cases of hypertension with or without secondary complications. This rise was most marked in cases of hypertension with cardiac involvement, in which the average level was 22.8 mg. per hundred cubic centimeters.

3. The average calcium level in seventy-five cases of hypertension with and without complications was normal (9.75 mg. per hundred cubic centimeters) as compared with that of the control group (9.8 mg. per hundred cubic centimeters).

4. The correctness of the observations on the normal amount of calcium in arterial hypertension was supported by the fact that the inorganic phosphorus level in these seventy-five cases (4.1 mg. per hundred cubic centimeters) showed no tendency to increase above the average amount of inorganic phosphorus in the controls (4.3 mg. per cent), while the calcium-inorganic phosphorus ratio of the seventy-five cases of hypertension (2.43) showed no tendency to fall below that of the control cases (2.33).

5. The potassium-calcium ratio rose from a control level of 2.03 in twenty-five control cases to 2.32 in seventy-five cases of hypertension with or without involvements. This rise was most marked in patients with hypertension and cardiac involvement (2.38) and least in patients with uninvolved hypertension (2.19).

6. The slight increase observed in the potassium level and in the potassium-calcium ratio observed in the cases of hypertension was probably due to impairment of the circulatory functions.

7. The cholesterol level rose from a control level of 171.6 to 204.5 mg. per hundred cubic centimeters in seventy-five cases of hypertension with or without involvements. This rise was most marked in patients with hypertension and renal involvement (227 mg. per hundred cubic centimeters) and least in patients with hypertension and cardiac involvement (194 mg. per hundred cubic centimeters). Of thirty-seven cases of uninvolved hypertension, only five (13 mg. per hundred cubic centimeters) showed an unexplainable hypercholesteremia.

8. There was no relation between the potassium-calcium ratio and the cholesterol content of the blood in hypertension.

9. Neither changes in the potassium-calcium ratio nor hypercholesteremia can be considered as playing a fundamental rôle in the development of arterial hypertension. Elevation of the potassium and cholesterol levels observed in one group of patients with hypertension is the result rather than the cause of changes in the cardiovascular system in arterial hypertension.

Dr. F. H. L. Taylor advised concerning the selection and adaptation of the chemical methods used in carrying on this investigation.

THROMBO-ANGIITIS OBLITERANS (BUERGER

VI. CHEMISTRY OF THE BLOOD *

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AND
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In a recently published paper,[1] we stated that there is a striking reduction in the volume of blood in thrombo-angiitis obliterans. In order to determine whether this reduced amount of blood is concentrated or normal, we studied the amounts of the individual chemical constituents in the blood. Determinations of the total amount of ash, total amount of proteins, chlorides, calcium, phosphorus, cholesterol, fasting sugar and the tolerance for sugar were made. In a small group of cases the specimens of blood were also subjected to a determination of fractional proteins in order to see whether any striking variation could be discovered.

REVIEW OF THE LITERATURE

A review of the literature on chemical studies of the blood in thrombo-angiitis obliterans is not illuminating, for in most instances the number of cases studied was few, and the conclusions drawn do not agree. Various investigators have focused their attention on one or more constituents, but no one has presented a complete chemical picture of the blood in an adequate number of cases. Bernhard [2] reported that the nonprotein nitrogen, calcium, cholesterol and chlorides were within normal limits and that in a few cases the blood sugar was elevated during fasting. Heitz [3] stated that the cholesterol was increased, ranging between 250 and 305 mg. per hundred cubic centimeters. Troisier and

* Submitted for publication, Jan. 2, 1931.

* From the Out-Patient Department and the Laboratories of the Mount Sinai Hospital.

* This work was aided by a grant from the Samuel Kellar Jacobs Research Fund for Thrombo-Angiitis Obliterans.

1. Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans (Buerger): IV. Reduction of Blood Volume, Arch. Int. Med. **45**:948 (June) 1930.

2. Bernhard, Adolph: Summary of the Chemical Blood Findings in Thrombo-Angiitis Obliterans, Med. Rec. **97**:430, 1920.

3. Heitz, Jean: De la cholesterinémie chez les sujets affectés d'arteritis obliterantes, Ann. de méd. **14**:378 (Nov.) 1923.

Ravina [4] likewise found increased cholesterol, averaging about 240 mg. per hundred cubic centimeters. Kuwabara,[5] quoted by Koyano,[6] reported normal figures for cholesterol and normal tolerance for sugar in the cases that he studied among the Japanese. Allen and Brown [7] reported normal figures for blood sugar and urea, and they are the only ones who found figures for cholesterol at the lower limit of normality. Meleney and Miller [8] studied the content of sugar during fasting and the tolerance for dextrose in 20 cases, and then found no striking variation from normal. Jablons [9] also found a normal tolerance for dextrose. He quoted Kahn's unpublished studies and stated that in 6 cases the calcium content was increased. Belegorodsky, quoted by Oppel,[10] found an increased content of calcium in the blood in this condition. In a personal communication, Dr. Alice Bernheim stated that she found the calcium level elevated. In his book,[11] aside from a reference to Koyano's paper, Buerger did not discuss the chemical constituents of the blood. The preponderance of evidence, therefore, seems to indicate that increased amounts of calcium and cholesterol are present and that the tolerance for sugar is normal.[12]

MATERIAL AND METHODS

The patients investigated had typical cases of thrombo-angiitis obliterans; they were selected at random from the large number being treated in the special clinic for this disease in the outpatient department of the Mount Sinai Hospital. The group represented all stages of the disease and various ages, and included both patients to whom treatment had been given and ones who had not received treatment. More than 100 cases were studied, but in order to avoid the inaccuracies that might have been present in the earlier determinations, the data of only the last forty cases are presented. A group of controls were studied to check the accuracy of our technic, and in each instance the figures obtained were within

4. Troisier, J., and Ravina, A.: La citrate de soude intravenieux dans la thrombo-angéite obliterantes, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:570 (May 15) 1924.

5. Kuwabara, M.: Beiträge zur Aetiologie der Spontangangrän an den Extremitäten, Kyoto Igaku Zassi **17**:61, 1920.

6. Koyano, K.: Clinical Study of 120 Cases of Thrombo-Angiitis Obliterans Among the Japanese, Acta scholae med. univ. imp., Kioto **4**:489, 1922.

7. Allen, E. V., and Brown, G. E.: Thrombo-Angiitis Obliterans, A Clinical Study of 200 Cases, Ann. Int. Med. **1**:535, 1928.

8. Meleney, F. L., and Miller, G. G.: Contribution to the Study of Thrombo-Angiitis Obliterans, Ann. Surg. **81**:976, 1925.

9. Jablons, B.: Thrombo-Angiitis Obliterans, Internat. Clin. **3**:193, 1925.

10. Oppel, V. A.: Gangrène spontanée et surrénalectomie, Lyon chir. **24**:1, 1927.

11. Buerger, Leo: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

12. Leibovici, R.: Etude chirurgicale des gangrènes juveniles, Paris, Gaston Doin, 1928.

TABLE 1.—*Chemical Constituents of the Blood in Forty Cases of Thrombo-Angiitis Obliterans*

Name	Date	Blood Volume per Kg., Cc.	Total Ash Content in Plasma, Gm. per 100 Cc.	Total Protein Content in Blood, Gm. per 100 Cc.	Calcium in Serum, Mg. per 100 Cc.	Phosphorus in Serum, Mg. per 100 Cc.	Chloride in Plasma, Mg. per 100 Cc.	Cholesterol in Plasma, Mg. per 100 Cc.
L. E.....	1/31/30	....	...	21.5	12.4	...	....	265
L. C.....	2/28/30	....	1.5	22.0	11.0	1.8	52.6	220
J. B.....	2/26/30	....	1.3	....	13.0	2.0	59.7	250
M. G.....	3/ 8/30	....	...	23.7	12.0	2.0	62.0	235
M. H.....	3/21/30	....	1.3	20.0	13.0	1.8	58.0	200
	3/25/30	....	1.4	21.2	12.0	2.0	58.5	185
J. W.....	4/14/30	....	1.3	....	11.9	1.9	52.6	210
W. B.....	4/15/30	63.7	1.0	22.5	11.9	2.0	50.0	235
	4/24/30	63.4	...	23.8	12.8	2.0	50.0	250
	8/25/30	....	1.2	22.5	12.5	2.0	51.5	250
J. G.....	4/17/30	71.8	1.3	....	12.0	2.0	52.6	250
M. W.....	5/14/30	46.3	1.7	21.0	12.2	1.8	52.6	220
	5/16/30	....	1.6	23.0	11.8	2.0	49.2	210
H. R.....	6/17/30	....	1.0	22.5	11.5	1.8	46.8	210
M. P.....	7/11/30	....	1.2	21.0	12.0	1.8	52.6	235
	8/ 6/30	....	1.1	21.9	12.0	2.0	52.6	235
L. K.....	7/15/30	....	...	23.1	12.0	2.0	52.6	235
	7/17/30	....	...	23.1	12.0	2.0	52.6	235
B. B.....	7/15/30	....	...	23.1	12.0	...	51.5	235
	7/17/30	....	...	22.5	12.0	1.8	52.6	265
D. S.....	7/25/30	....	...	22.5	12.5	2.0	51.5	235
	7/28/30	....	...	23.1	13.0	2.0	52.6	235
D. P.....	7/28/30	68.0	...	22.5	13.0	1.8	52.6	200
M. F.....	7/28/30	66.0	...	23.1	13.0	1.8	52.6	250
	7/30/30	....	...	23.8	12.0	2.0	51.5	250
R. M.....	8/25/30	....	1.1	22.5	12.5	2.0	52.6	235
	9/10/30	....	1.1	22.5	13.0	2.0	51.5	235
J. M.....	8/29/30	65.2	1.2	23.1	13.0	1.8	46.8	265
J. W.....	9/ 5/30	58.0	1.5	24.4	12.5	2.0	52.0	210
H. Z.....	2/10/30	75.0	1.2	23.8	12.0	1.3	58.5	210
E. Z.....	2/10/30	....	1.2	23.0	11.7	1.2	59.7	210
H. L.....	2/ 3/30	69.0	...	....	13.6	1.4	63.1	240
E. M.....	2/24/30	69.8	...	23.8	12.4	2.5	58.5	270
	8/29/30	65.0	1.2	23.8	12.5	1.9	56.0	265
J. S.....	9/ 8/30	50.0	1.3	23.8	13.0	1.5	55.0	250
N. G.....	2/ 5/30	....	...	22.5	11.9	1.7	55.0	230
B. F.....	2/10/30	....	1.3	20.0	12.8	1.4	58.5	270
	2/28/30	....	1.2	22.5	12.0	2.0	56.1	220
D. K.....	2/10/30	....	1.0	20.6	10.8	1.5	59.7	230
	3/17/30	....	1.3	22.5	11.4	...	64.0	220
E. L. J....	2/21/30	....	1.2	22.5	12.0	1.7	64.0	235
A. L.....	2/26/30	58.3	1.0	24.0	12.6	1.9	55.0	210
J. S.....	2/22/30	62.4	1.0	24.0	12.0	...	58.5	210
	9/ 6/30	52.0	1.3	25.0	13.0	1.8	58.5	220
C. K.....	2/24/30	65.2	...	....	12.2	2.0	58.5	195
	9/ 5/30	53.0	1.3	24.4	13.0	2.0	55.0	250
T. Z.....	6/ 4/30	64.8	1.2	....	11.5	2.0	52.6	250
	8/20/30	54.0	1.3	21.8	12.0	2.0	52.6	250
J. F.....	9/ 8/30	53.0	1.3	23.1	12.0	1.9	50.3	235
H. E.....	3/12/30	68.0	0.9	22.5	12.0	1.8	....	235
	8/20/30	62.0	...	....	12.5	1.8	51.5	210
B. L.....	3/19/30	62.0	1.2	23.4	13.3	2.2	67.8	270
M. W.....	4/ 2/30	53.0	1.2	22.5	11.6	1.9	55.0	210
B. R.....	4/14/30	71.0	1.1	23.0	12.0	2.0	53.8	210
B. S.....	8/14/30	....	1.3	22.5	13.0	2.0	51.5	265
H. G.....	8/18/30	....	1.2	23.8	13.0	2.0	52.6	270
B. B.....	8/18/30	56.0	1.2	23.8	14.0	1.8	52.6	265
D. L.....	8/21/30	60.0	...	23.1	14.0	1.8	56.0	250
Average.....		61.6	1.2	22.8	12.4	1.9	54.7	235

the accepted range of normal. All of the patients and the subjects used as controls were males. All determinations were made on specimens of blood obtained in the morning before the patient had broken his fast.*

The determinations of the total amount of ash were made after evaporating and ashing from 2 to 5 cc. of plasma. The total nitrogen content was obtained by the Kjeldahl macroscopic and microscopic methods, and the total protein content was computed by multiplying by 6.25.[13] Determinations of calcium were made by the Clark-Collip modification of the Kramer-Tisdall method.[14] To insure com-

TABLE 2.—*Chemical Constituents of the Blood in Twenty-One Normal Persons*

Name	Date	Blood Volume per Kg., Cc.	Total Ash Content in Plasma, Gm. per 100 Cc.	Total Protein Content in Blood, Gm. per 100 Cc.	Calcium in Serum, Mg. per 100 Cc.	Phosphorus in Serum, Mg. per 100 Cc.	Chloride in Plasma, Mg. per 100 Cc.	Cholesterol in Plasma, Mg. per 100 Cc.
A. F.	2/12/30	....	...	....	10.0	...	41.0	135
B. S.	2/18/30	....	0.9	18.8	10.2	1.9	52.6	135
C. B.	3/ 8/30	....	...	15.0	10.6	1.8	46.8	150
S. S.	3/ 8/30	....	...	15.0	10.2	2.0	47.0	185
I. M.	4/ 9/30	....	...	18.8	9.0	2.0	40.1	180
S. G.	6/ 4/30	....	1.0	15.0	9.7	2.0	52.6	170
H. S.	6/ 4/30	....	1.0	16.8	10.2	2.0	52.6	185
A. A.	6/12/30	....	1.0	20.0	10.5	2.8	49.0	185
A. K.	6/12/30	....	0.9	15.0	10.1	2.7	47.9	150
W. L.	6/12/30	....	1.0	13.5	10.2	2.8	46.8	150
E. S.	6/12/30	....	0.9	17.5	10.1	2.8	46.8	170
F. K.	8/ 4/30	....	0.9	18.8	8.0	2.8	46.8	165
T. N.	8/28/30	....	0.9	18.8	10.0	3.0	52.6	165
Average			0.9	16.9	9.9	2.4	48.6	165
V. V.*	2/28/30	....	1.2	18.8	8.4	2.5	46.8	265
G. G.*	3/12/30	....	...	25.0	10.0	2.5	65.0	220
	3/28/30	....	...	23.0	11.2	2.0	58.5	270
	8/27/30	....	1.0	21.3	10.5	2.0	52.6	270
W. H.*	4/17/30	....	0.9	18.8	10.9	1.9	56.0	170
D. K.*	6/19/30	....	1.0	21.0	10.5	2.0	46.8	265
S. U.*	7/ 1/30	....	1.0	23.1	11.0	2.0	51.5	270
H. S.*	7/ 8/30	....	1.0	23.1	11.0	2.0	51.5	270
H. S.*	8/ 4/30	....	1.0	20.0	11.0	2.5	51.5	250
I. G.*	8/28/30	....	1.0	20.0	10.5	3.0	51.2	265
Average			1.0	21.4	10.5	2.2	53.1	250

* These patients were heavy smokers. The high figures for the total protein and cholesterol content are noteworthy.

plete precipitation of the calcium, the mixture of serum ammonium oxalate was allowed to stand for twenty-four hours. Studies on phosphorus were made by the Kuttner and Lichtenstein method.[15] Figures for cholesterol were obtained by the Sackett modification of Bloor's method.[16] Chlorides were studied by the

13. Hawk and Bergeim: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, 1927, p. 711.

14. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

15. Kuttner, T., and Lichtenstein, L.: Micro Colorimetric Studies: Estimation of Phosphorus, J. Biol. Chem. **86**:671, 1930.

16. Sackett, Guy E.: Modification of Bloor's Method for the Determination of Cholesterol, J. Biol. Chem. **64**:203, 1925.

method of Van Slyke,[17] and the sugar content, by the modified Folin-Wu method.[18] Tests for sugar tolerance were made after the administration of sugar by both the oral and the intravenous method.[19]

RESULTS

Total Ash Content.—The inorganic content of the plasma was determined by evaporating a known amount of plasma in an oven to a dry weight, and then incinerating it until all organic matter was consumed. A normal figure for the total ash content is about 0.9 Gm. per hundred cubic centimeters, and from 0.8 to 1 Gm. may be taken as the limits of normal variations. Forty determinations of the total ash content in patients with thrombo-angiitis obliterans gave

TABLE 3.—*Determination for Fractional Plasma Protein in Ten Persons with Thrombo-Angiitis Obliterans and Four Normal Persons*

Patients with Thrombo-Angiitis Obliterans	Fibrin, per Cent	Albumin, per Cent	Globulin, per Cent
A. R.	0.48	4.90	2.50
T. Z.	0.53	5.29	2.29
M. K.	0.58	4.77	2.69
J. B.	0.37	5.04	1.82
A. S.	0.57	4.82	1.99
B. S.	0.65	6.03	3.38
S. R.	0.64	5.18	3.38
I. G.	0.51	5.72	2.31
B. R.	0.62	5.71	2.76
W. Z.	0.66	5.94	2.47
Normal Subjects			
Dr. G.	0.48	5.28	2.18
Dr. S.	0.37	5.22	2.10
Dr. K.	0.42	5.22	2.60
Dr. S.	0.46	5.82	2.48

an average of 1.2 Gm., as compared to 0.9 Gm. in ten control subjects. Thus the ash content reveals an average increase in mineral constituents of more than 30 per cent. Total solids, as determined by dry weight, show a similar increase.

Total Protein Content in the Blood.—The total amount of nitrogen in the blood was determined by the standard macroscopic and microscopic Kjeldahl methods. The total protein content was estimated by multiplying by 6.25 the figure obtained. The normal range of total proteins in whole blood has been estimated as being from 15 to 20 Gm. per hundred cubic centimeters.[2] In our group of control cases the

17. Van Slyke, Donald D.: Determination of Chlorides in Blood and Tissue. J. Biol. Chem. **58**:523, 1923.

18. Folin, Otto, and Wu, Hsien: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

19. Woodyatt, R. T.: Timed Intravenous Injections of Glucose at a Lower Rate, J. Biol. Chem. **30**:155, 1917.

average figure was 16.9 Gm. per hundred cubic centimeters. In the 40 cases of thrombo-angiitis obliterans, the range was from 20 to 25 Gm. per hundred cubic centimeters. Thus, with an average of 22.8 Gm. per hundred cubic centimeters, there is an increase in the total protein content of the blood of approximately 30 per cent. In 10 cases, a fractional protein analysis was made on the plasma. An increase in all constituents was apparent, but it was more striking in the fibrinogen fraction (table 3).

Calcium and Phosphorus.—One of the striking alterations that we found in the patients with thrombo-angiitis obliterans was the uniform increase in the calcium content of the serum. In the 40 cases reported, this elevation was clearly illustrated (table 1). The average figure obtained in the subjects used as controls was 9.9 mg. per hundred cubic centimeters, which agrees with the figures obtained by other investi-

TABLE 4.—*Blood Sugar in Fifty-Three Fasting Patients with Thrombo-Angiitis Obliterans*

Mg. per 100 Cc.	Number of Cases
60-69	4
70-79	14
80-89	11
90-99	11
100-110	13
Total	53

gators. In the patients with thrombo-angiitis obliterans, the determinations for calcium by the same method ranged from 10.5 to 13 mg., with an average of 12.4 mg. per hundred cubic centimeters. Associated with this elevation in the level of calcium was a decrease in the figures for phosphorus (table 1).

Cholesterol.—Another consistent alteration noted in the chemical analysis of the blood was an appreciable elevation in the level of cholesterol in the plasma. The figures ranged from 210 to 265 mg., with an average at about 235 mg. per hundred cubic centimeters. Determinations made by the same method on normal subjects averaged 165 mg. per hundred cubic centimeters.

Chlorides and Sugar.—In a few cases the chlorides in the plasma showed a slight increase over the normal (from 45 to 55 mg. per hundred cubic centimeters), but for the most part they may be classed as high normal. Studies made on fifty-three fasting patients showed the level for sugar to be normal (table 4). In 37 cases a study of the tolerance for sugar after its administration by mouth was made, and in 14 cases, after the intravenous injection of dextrose; these tests failed to show any striking abnormality.

COMMENT

From a study of the data presented, the general trend is unmistakable. It is readily apparent that the amounts of organic and mineral matter present in the blood are greater than normal, and that they are roughly equivalent to an increase of about 30 per cent over the figures obtained for our control cases. Since our determinations for the volume of blood in patients with thrombo-angiitis obliterans reveal a decrease of from 20 to 25 per cent, it can be stated that with this decrease in volume there is a tendency to an increase in density or concentration. This would suggest that a curious process of chronic dehydration is one of the factors present in thrombo-angiitis obliterans. A study of the water metabolism in some of our cases (to be published later) shows abnormalities which may throw some light on this point. That concentration is not the only factor is also apparent from the fact that with elevation of the figures for calcium there is a diminution in the phosphorus.

SUMMARY AND CONCLUSIONS

A chemical analysis of the blood of forty patients with thrombo-angiitis obliterans was studied to determine the total ash content, total protein content, calcium, phosphorus, chlorides, sugar and the cholesterol content.

Increases in the total ash content, total protein, and in the calcium and cholesterol were noted. No striking abnormalities were found in the determinations for chlorides and sugar. Tests for tolerance of sugar gave normal results.

The conclusion that there is a tendency to concentration of the blood in thrombo-angiitis obliterans seems warranted.

CUTANEOUS LESIONS ASSOCIATED WITH A DEFICIENCY IN VITAMIN A IN MAN*

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During the winter and spring of 1928 and 1929 many cases of keratomalacia were seen in the hospital of the Peiping Union Medical College. Most of these occurred among Chinese soldiers, garrisoned in villages in the vicinity of Peiping, who had subsisted for various periods of time on inadequate diets, deficient particularly in animal proteins and fats.

In addition to the classic signs of keratomalacia, the majority of these patients manifested certain cutaneous lesions of such uniform character as to suggest their being of more than coincidental significance. This assumption was given further support by the fact that they were analogous histologically to the pathologic changes in the eye and in other tissues of animals and man following deprivation of fat-soluble vitamin A. As a rule the lesions of the skin preceded the appearance of keratomalacia and responded to dietary therapy simultaneously with the ocular lesions, although much more slowly. None of the patients showed signs of beriberi, pellagra or scurvy.

The fifteen cases constituting the material on which this report is based were first studied in the ophthalmologic clinic, where the diagnosis made was typical keratomalacia of from two weeks to three months' duration. In reporting observations on these and earlier cases, Pillat [1] emphasized the identity of the ocular lesions with those found in infants and children under similar conditions of malnutrition. He also called attention to the generalized manifestations of deficiency in vitamin A among these patients, including involvement of the skin. Cutaneous lesions have hitherto not been described in connection with nutritional ophthalmia, although Bloch [2] observed a dry, shriveled, scaly condition of the skin among infants affected with the disease, and Wilson

* Submitted for publication, Dec. 31, 1930.

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1. Pillat, A.: Does Keratomalacia Exist in Adults? Arch. Ophth. **2**:256 (Sept.) and 399 (Oct.) 1929.

2. Bloch, C. E.: Ugesk. f. læger **79**:1516, 1917.

and DuBois,[3] among others, reported in association with keratomalacia a condition somewhat similar to that not infrequently present in patients with severe malnutrition without signs of xerophthalmia.

All fifteen patients of this series were soldiers, with the exception of one, a pedler, and were admitted to the hospital during February, March and April, 1929. Their ages ranged from 19 to 33 years, the majority being in the early part of the second decade. Each gave a history of having lived on a poor and monotonous diet for periods of from six months to one or more years. The diets consisted chiefly of rice, maize, millet, occasionally a poor grade of wheat flour, white cabbage and salted vegetables. Meats, eggs and green vegetables were rarely eaten; a few patients had never had these articles of food, and others had had them not more often than once a month. Usually the quantity of food was sufficient, but there is reason to believe that the diet in many cases was much poorer both in quality and amount than was reported. The better paid officers who were able to supplement the regular ration were not affected by the disease.

In this connection it is well to call attention to the main features of the ordinary Chinese diet. In an extensive study of the foodstuffs utilized in the common diet of several groups of the Chinese middle classes in Peiping, Wu and Wu[4] have observed that the average diet is adequate in caloric value but below the optimum in proteins and in vitamins A and D, and low in calcium and phosphorus. Vitamins B and C are probably present in adequate amounts. Practically all the fats and oils used for dietary purposes are of vegetable origin; milk, butter and other dairy products are almost never used. It is clear, therefore, that even under ordinary circumstances of civil life, the Chinese dietary is low in vitamin A.

HISTORY OF SYMPTOMS

The natural history of the development of the lesions of the skin was as follows: Several weeks prior to the onset of the ocular symptoms, the skin became dry and slightly rough. Subsequently, spinous papules appeared at the sites of the hair follicles, first involving the anterolateral aspect of the thighs and the posterolateral aspect of the upper part of the forearms. The eruption gradually spread to the extensor surface of both upper and lower extremities, the shoulders and the lower part of the abdomen, and to a less extent to the chest, back and buttocks. In some cases the skin was darker than normal, turning a dull slate color. There was absence of visible sweating, and the

3. Wilson, J. R., and DuBois, R. O.: Keratomalacia in an Infant, with Postmortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923.

4. Wu, H., and Wu, D. L.: Chinese J. Physiol. Rep., ser. 1, 1928, p. 135.

articular folds, which are usually moist, were dry and covered with closely adherent, delicate scales. The normal markings on the surface of the skin were exaggerated in places, giving it a finely wrinkled appearance.

The follicular papules varied in size according to the stage of development and the degree of perifollicular infiltration. The largest were approximately 5 mm. in diameter, hemispherical, rather firm and usually deeply pigmented. The hyperpigmentation extended in a narrow zone beyond the base of the lesion. Each papule held in its apex a keratotic plug which in most instances projected above the surface of the lesion as a hard spinous process, or was covered by a loosely adherent scale that bridged the occluded follicular recess. When expressed, the plugs left gaping central craters in the summits of the papules. The eruption was usually abundant and symmetrical, but occasionally the lesions were few and widely scattered, or more rarely, restricted to a single area.

In five cases there was a marked tendency to pustulation, usually on the extremities, leading to the formation of ecthymatous ulcers. Although as a rule there were not over four or five such ulcers, in one case they were so numerous and so sharply formed as to resemble secondary ulcerative syphilids. Cultures of *Staphylococcus aureus* and *Streptococcus hemolyticus* were obtained from the ulcers in several cases. Scabies was a complicating infection in four instances.

Large numbers of conspicuous comedones were present on the face at the sites commonly involved by acne. In one case, that of a patient 28 years of age, these were the only lesions of the skin besides the general xerosis. A few acneiform papules were also distributed over the same areas. Unlike acne, the skin of the face was dry and without any sign of excessive sebaceous secretion. Occasionally it had a puffy appearance suggesting edema.

The hair was dry but otherwise normal. No remarkable changes in the nails were observed, although two patients had slight transverse ridging of a single nail on each hand. Other than a slate-colored pigmentation of the buccal and lingual mucosa in one patient, and a mild atrophic rhinitis in another, the mucous membranes of the oral and nasal cavities showed no visible variation from the normal.

Examination of the nervous system did not reveal any significant abnormality, and there was no instance of cardiovascular disease in this group of cases. Two patients had pulmonary tuberculosis, and three an acute tracheitis or bronchitis. One of the patients with pulmonary tuberculosis was thought also to have tuberculosis of the intestine. This was the only case in which there were gastro-intestinal symptoms.

Ova of *Ascaris* were found in the stools of eight patients, ova of hookworm in five and cysts of *Entamœba histolytica* in one. Four of the fifteen patients were apparently free from intestinal parasites.

Chemical and microscopic examination of the urine gave negative results, with the exception of the patient with advanced tuberculosis, whose urine contained a trace of albumin. This patient also had edema of both feet and ankles of two months' duration, and a severe secondary anemia. Four other patients had anemia of moderate degree. The Wassermann and Kahn tests of the blood gave positive results in two cases, neither of which showed active manifestations of syphilis.

RESULTS OF TREATMENT

After admission to the hospital, the patients were observed for periods of from one week to two months. During this time they were fed a well balanced Chinese diet, chiefly vegetarian, to which were added liver, butter and eggs Cod liver oil was administered daily in quantities of 30 cc. Each patient also received one lemon a day. In order not to modify the cutaneous lesions, no local medication was employed, and baths were restricted to the minimum required for cleanliness.

Under this regimen there was rapid improvement in the keratomalacia, although there was but little restoration of vision in cases of advanced degeneration of the cornea. In the cases in which the patient was under dietary treatment for two weeks or more, moisture of the skin was definitely increased, and in several visible sweating was observed. Ulcerative lesions healed promptly and completely. The keratotic papules decreased in size more slowly, and many of the central cornified plugs were extruded. In the cases in which the eruptive lesions completely disappeared, delicate atrophic scars, surrounded by a zone of brownish pigmentation, remained at the follicular orifices. Two months was the longest period any patient was under observation, which was not sufficient time for the skin to regain its normal appearance and texture.

Histologic examination of the cutaneous lesions in various stages of growth showed the pathologic process to be essentially one of hyperplasia and hyperkeratinization of the epithelium of the epidermis and hair follicles, with associated metaplasia of the epithelium of many of the sweat ducts to the keratinizing type, degeneration of the glandular structures of the skin and infection.

The horny layer was moderately hypertrophied and of homogeneous structure. The mouths of the hair follicles were greatly dilated by dense masses of horny substance arranged in more or less concentric lamellae. These either projected from the follicles or were flush with

the surface and covered by a continuation of the horny layer. Nuclei were not present in any of the cornified cells. Coiled atrophic hairs were found in some of the follicular plugs. In the region of the hair follicles, and in other areas of epithelial hyperplasia, there was a definite increase not only in the amount of intracellular pigment but in the number of pigment-bearing cells. Very few chromatophores were found in the corium.

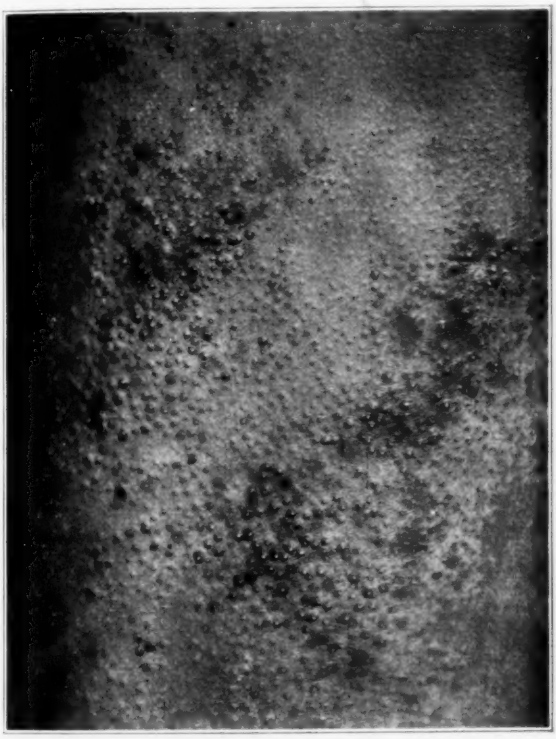

Fig. 1.—Area of skin on the thigh showing follicular papules with projecting horny spines and hyperpigmentation.

The lower part of the hair follicles was atrophic, and in some places the tip was completely severed from the rest of the follicle by rather dense connective tissue. On the study of serial sections, the detached segments were found to be occasionally cystic and filled with desquamated epithelial cells. Surrounding such follicles, and to a less extent those in which the keratosis was minimal, were fairly well circum-

scribed areas of loose reticular tissue containing lymphocytes, fibroblasts and occasional endothelial cells. Numerous blood capillaries were present in these areas.

In the sections examined no normal pilosebaceous structure was seen, and only a few remnants of sebaceous glands were found in the midst of the inflammatory zones. The mouths of many of the sweat ducts were dilated and occluded by conical masses of keratinous material. In places the epithelial lining of the upper part of the ducts

Fig. 2.—Same area as that in figure 1, showing residual pigmentation and scars at follicular orifices two months after dietary therapy was commenced. The large scar at the lower part of the picture followed a biopsy wound.

was increased in thickness and was desquamating. The epithelial cells of the tubules were frequently shrunken and irregular, or the lumen of the glands was dilated and the epithelium greatly compressed.

Pustulation occurred primarily in the follicular plugs and from there extended into the perifollicular tissues. The earliest sign of

ulceration was found in the walls of the distended hair follicles. Hemorrhage did not occur about the follicle or elsewhere in the skin.

A comparison of the changes in the skin of these patients with those in the eye and related structures in human and experimental cases of keratomalacia is of particular interest and offers strong presumptive evidence of the specific nature of the cutaneous lesions. In keratomalacia, according to Mori [5] and others, there is cornification of the conjunctival and corneal epithelium and, in the later stages, hyperplasia of the epithelial cells of these structures. The keratinizing process extends into the ducts of the para-ocular glands, and the acini may undergo complete disintegration with conversion of the gland into a series of cavities lined by stratified epithelium and filled with desquamated cells. There is an accompanying element of infection, which in the terminal stages of the process constitutes a major factor in the production of corneal disintegration.

In a study of the pathologic changes in rats fed on diets deficient in fat-soluble A, Wolbach and Howe [6] concluded that the specific morbid process is a widespread keratinization and replacement of many different epithelia by stratified keratinizing epithelium, which they observed in various parts of the respiratory and alimentary tracts, in the eyes and para-ocular glands and in the genito-urinary tract. They were of the opinion that the loss of secretory function in various glands throughout the body and the distinctive changes observed in other tissues were due to the mechanical factors consequent to the formation and retention of the desquamated epithelial cells.

From the study of the patients observed in Peiping with respect to the sequence in which the various pathologic changes occurred in the skin, it appears that the primary process was an excessive epithelial keratinization, resulting in the mechanical occlusion of hair follicles and sweat ducts, and in secondary degeneration of the sebaceous and sweat glands. Necrosis was a terminal event presumably dependent on the decreased resistance of the tissues to infection.

Cutaneous lesions essentially identical to those of this series of cases have been described by Nicolau,[7] Willshire [8] and others as a manifestation of scurvy. In correlating changes in the tissues with deficiency in a specific vitamin it should be remembered that single dietary faults rarely occur alone, as a diet that is lacking in one factor

5. Mori, S.: Primary Changes in the Eyes of Rats Which Result from Deficiency of Fat-Soluble A in Diet, J. A. M. A. **79**:197 (July 15) 1922; Bull. Johns Hopkins Hosp. **33**:357, 1922.

6. Wolbach, S. B., and Howe, P. R.: J. Exper. Med. **42**:753, 1925.

7. Nicolau, W.: Ann. de dermat. et syph. **7**:399, 1918-1919.

8. Willshire, H.: Lancet **2**:564, 1919.

is generally deficient in others. It is doubtful whether an uncomplicated deficiency disease ever exists in man, and it is only by carefully planned experimental diets that a specific deficiency disease can be produced in animals.

In view of such facts, one may question the justification of assuming any causal relationship between the deficiency of vitamin A in the diets of the patients at Peiping and the cutaneous lesions; nevertheless, the essential changes in the skin, when compared with those produced in experimentally controlled cases of disease due to deficiency in vitamin A were of such nature as to suggest their being a part of this specific syndrome rather than of that produced by deficiency in other vitamins.

CALCIUM AND PHOSPHORUS METABOLISM IN A CASE OF NONTROPICAL SPRUE WITH ASSOCIATED TETANY *

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During the course of investigations of various disorders of calcium and phosphorus metabolism, we had the opportunity of studying a patient with nontropical sprue complicated by tetany. The association of sprue with tetany is probably not so common as was once supposed. In reviewing the literature, one finds that a number of such cases have been reported. In some of these reports no mention is made of the values of the serum calcium or serum phosphorus. A search of the literature failed to reveal any report bearing on the total calcium and phosphorus metabolism in this disease syndrome. Analysis of the data reported in this case shows why the resultant tetany was secondary to the long-standing diarrhea and not related to parathyroid deficiency.

REPORT OF CASE

History.—A man, aged 39, married, a Jewish physician, was admitted to the metabolism ward of the Massachusetts General Hospital on Dec. 4, 1928, complaining of diarrhea of three years' duration. The family history revealed nothing of note. The past history showed that for years he had been subject to frequent colds and infections of the upper respiratory tract with symptoms suggesting chronic bronchitis. In late years he had suffered a great deal from chronic sinusitis, with occasional, acute flare-ups. He had never been out of the United States.

The present illness could be traced back as far as eight years before admission. At this time the patient first noted a slight loss of strength and that he became fatigued more readily than normally. Owing to worries about his home and the demands of a scattered medical practice in Chicago, his habits of living, eating, sleeping, etc., were irregular. Three and one-half years before admission he began to lose weight rapidly, and his weight decreased from a normal 150 pounds

* Submitted for publication, Nov. 28, 1930.
* Read before the American Society for Clinical Investigation, May 4, 1931.
* From the Medical Clinic of the Massachusetts General Hospital and the Department of Medicine of Harvard Medical School.
* The expenses of this investigation were aided in part by grants from the De Lamar and William W. Wellington Memorial Research Funds of Harvard Medical School.

to about 130 pounds (from 68 to 59 Kg.) During this time, the bowel movements varied from mushy to formed stools.

Three years prior to admission he suffered from a sudden onset of watery diarrhea, with as many as twenty stools a day, which, with remissions, persisted until he entered the Massachusetts General Hospital. Remissions had been few, incomplete and secured only by complete rest, warm weather and a low intake of fluids. The acute exacerbations of diarrhea were usually preceded by acute infections of the upper respiratory tract, chiefly ethmoiditis and maxillary sinusitis. Throughout the three years he noted a gradually increasing pallor of the skin and of the mucous membranes; at times there had been moderate edema of the lower extremities. For the past year, there had been periods of soreness of the tongue at the time of the acute exacerbations of diarrhea. Four months before admission, he suffered from a severe attack of diarrhea following ethmoiditis. From this time until admission, a new train of symptoms arose, viz., tetany, polyuria and perversion of taste and appetite. He lost weight steadily and became progressively weaker and more emaciated. Prior to his stay in this hospital he had been observed in Chicago at the Michael Reese, the North Chicago, the Washington Boulevard, the Presbyterian and the Billings Memorial Hospitals. At the Presbyterian Hospital, he was under the care of Dr. Wilbur E. Post from Nov. 29 to Dec. 19, 1927. At this time (a year before we saw him) his stools were watery, acid or neutral in reaction, and contained no blood and very little mucus. A yeastlike organism was found in both the sputum and the stools. The course of the disease was febrile, with cough, sputum and pleuritic pains in the right side of the chest. Roentgenograms of the chest suggested a marked degree of bronchiectasis at the base of each lung.

About six weeks after his discharge from the Presbyterian Hospital, he entered the Billings Memorial Hospital, where from Jan. 28 to Feb. 14, 1928, he was on the service of Dr. Walter L. Palmer. Recorded data at this institution included: weight, 83 pounds (37.6 Kg.), essentially normal temperature, normal urine and 3,280,000 erythrocytes per cubic millimeter. On examinations the sputum did not show tubercle bacilli. Roentgenograms of the chest showed fibrosis of the right lung, representing "a healed pyogenic process, either an old pneumonia or bronchopneumonia, or an old interlobar pleurisy." A series of roentgenograms of the gastro-intestinal tract did not show any abnormality. After discharge, the patient failed to return to the Billings Memorial Hospital for follow-up study until October, 1928. At this time, though he was stronger and heavier, occasional carpopedal spasms had developed. Studies of the blood showed the serum calcium to be 5.7 mg. per hundred cubic centimeters. During the administration of Collips' parathyroid extract and calcium lactate, the value rose to a level of 7.8 mg. per hundred cubic centimeters. The diagnosis at the time of the patient's discharge from the hospital was probable nontropical sprue.

Physical Examination.—At the time of entrance to the Massachusetts General Hospital, physical examination showed a pale, emaciated man of slight build, weighing 33 Kg., with sunken eyes, a dry and inelastic skin, a negative Chvostek's sign, a positive Trousseau's sign and occasional carpopedal spasms. The tongue protruded in the midline. It was smooth, with red, raw-appearing edges. Most of the teeth were missing, and those that remained were carious. Examination of the chest showed limited expansion of the right lung with diminished excursion of the diaphragm on the right side. There were occasional crepitant râles at the base of both lungs, but friction rubs were not heard. There was slight pitting edema about both ankles.

Laboratory studies showed: red blood cells, 2,260,000; white blood cells, 17,300, and hemoglobin (Tallquist), 50 per cent; a blood smear examination was normal except for slight achromia of the red blood corpuscles. The latter were found to be normal in size, averaging 7.8 microns (median figure) in diameter; none was nucleated or stippled. The urine showed a slight trace of albumin, but nothing else that was abnormal. The bowel movements averaged four a day at first; the stools were usually large, light brown, watery or mushy, and were acid in reaction. There was a definite odor of yeast. Microscopically, there was an excess of neutral fat and fatty acid crystals and a moderate number of undigested muscle fibers. The guaiac test at times gave a moderately positive reaction and at other times, a negative reaction. Bacteriologic study of the stools revealed, in addition to yeastlike organisms, a growth of *B. coli*. Direct smear showed that from 20 to 30 per cent of all of the organisms were yeasts. On January 30, the total fat content of the wet stool was 9.38 per cent. The pancreatic ferments were determined by a study of the duodenal juice; though the proteolytic and amylolytic enzymes were found to be normal, lipolytic enzyme activity could not be demonstrated. The method of McClure and his associates [1] was used for the estimation of the activity of the pancreatic ferments. The results of a gastric analysis,

TABLE 1.—*Gastric Analysis After Several Weeks of Treatment with Liver*

	Fasting	15 Minutes After Test Meal*	30 Minutes After Test Meal	45 Minutes After Test Meal
Free hydrochloric acid	0	0.0	0	0
Total acid†	4	7.0	9	10
Chlorides‡	41	32.5	48	..

* The test meal consisted of 100 cc. of 7 per cent alcohol; 1 cc. (0.5 mg.) of ergamine acid phosphate was administered subcutaneously at the same time.

† Acidity is expressed in cubic centimeters of tenth-normal acid per hundred cubic centimeters of gastric contents.

‡ Chlorides are expressed as cubic centimeters of tenth-normal per hundred cubic centimeters of gastric contents.

performed on March 15 (several weeks after there had been improvement through liver therapy), are given in table 1.

Chemical studies of the blood showed: sugar during fasting, 88 mg.; nonprotein nitrogen, 26 mg.; total protein, 5.94 Gm. per hundred cubic centimeters, and an icteric index of 3. On the morning after admission, the serum calcium was 6.7 mg. and the serum phosphorus 1.28 mg. per hundred cubic centimeters. The sputum, at times moderately abundant, was yellowish, tenacious and blood-streaked. Microscopic examination showed many pus cells and bacteria of various types, but no yeastlike forms or tubercle bacilli were found. Culture of the sputum showed the predominant organisms to be pneumococci.

Roentgen studies showed a diminution of lime salts in the bones, maxillary sinuses that were less radiant than normal and changes in the chest which suggested "encapsulated fluid, probably interlobar on the right side and a chronic pathological process at the right base."

Course.—At the time of entry the patient was seriously ill and difficult to manage; therefore, the diet was not kept so constant as in our previous metabolism

1. McClure, C. W.; Wetmore, A. S., and Reynolds, L.: New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch. Int. Med. **27**:706 (June) 1921.

studies.[2] Because of this difficulty, the diet was ordered "as desired," but in general it was semisolid, low in fat and high in calcium, phosphorus, protein and vitamins. It included a large amount of milk (from 800 to 2,000 cc. a day). The intake of calcium per day varied from 0.6 to 4.3 Gm. The ratio of calcium to phosphorus in the diet varied from 1:1 to 1.2:1. The intake of fluid varied from 1.9 to 3.8 liters, while the urinary output varied from 1.15 to 2.15 liters per day.

Six days after admission, the administration of liver extract (Lilly no. 343) was begun in doses of 6 vials a day. After twenty-four days, the dose was reduced to 3 vials a day and was so continued until February 16. From this time until late in the summer of 1929, the patient did not receive liver extract, but during this period a small amount of fresh liver was included in the diet. The

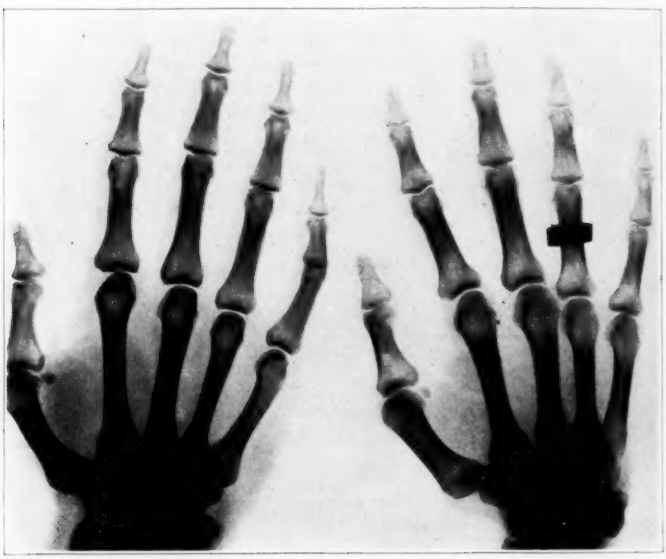

Fig. 1.—Roentgenogram of the patient's hand (right) as compared with that of a normal person (left). Note the generalized decalcification.

administration of iron by mouth was begun on January 2, and increased thereafter, so that from January 24 he received 24 grains (1.56 Gm.) of reduced iron a day, and, except for occasional periods, he had continued to take large doses of iron.

The most striking index of improvement is to be seen in the curve for body weight (fig. 2). Starting at a level of 32.6 Kg. on December 4, there was a precipitous rise to the level of 49.8 Kg. on January 24. Then followed a period

2. Albright, F., and Bauer, W.: The Action of Sodium Chloride, Ammonium Chloride, and Sodium Bicarbonate on the Total Acid-Base Balance of a Case of Chronic Nephritis with Edema, J. Clin. Investigation **7**:465 (Aug.) 1929. McClure, Wetmore and Reynolds (footnote 1).

in which there was a loss of weight due to a flare-up in the condition of the chest. Following this there was again a consistent rise until the patient's discharge on March 20, at which time the weight was 50.4 Kg. This continued in the month following discharge, so that when the patient was seen on April 20, his weight was 61.4 Kg.

Coincident with this gain in weight, improvement was evident in other respects. The diarrhea gradually decreased in severity, so that after the patient had been in the hospital for two weeks, he had only one or two bowel movements a day (though the character of the stools changed very little). Further frequency of bowel movements was not noted during his stay in the hospital, except for short exacerbations from February 11 to February 16, and on March 19 and 20, the date of discharge.

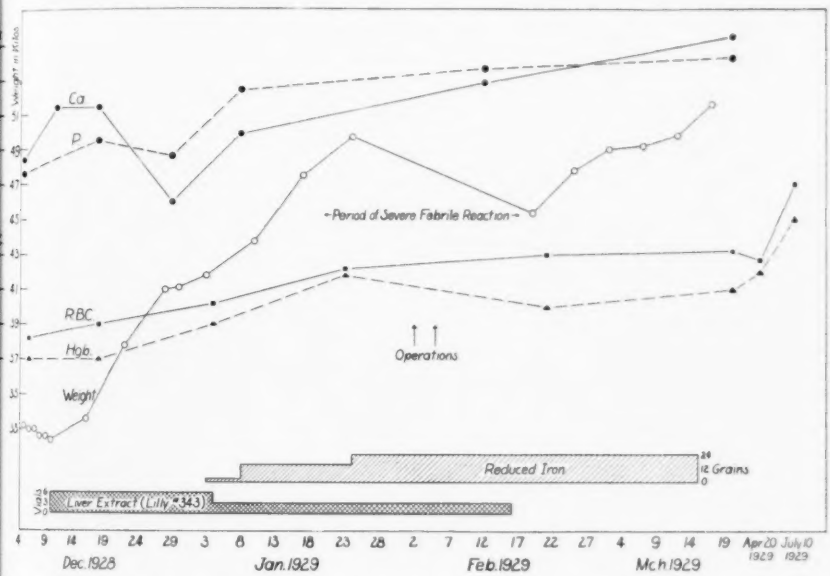

Fig. 2.—Chart showing the response of the serum calcium, serum phosphorus, erythrocyte count, hemoglobin and body weight to treatment.

It is noteworthy that despite the administration of 6 vials of liver extract from December 11 to January 4, during that time the erythrocytes rose only from 2,260,000 to 2,570,000 per cubic millimeter, and the hemoglobin from 50 to 60 per cent. Our data regarding the reticulocyte count during liver therapy are too incomplete to report. By February 21, the erythrocytes and hemoglobin reached a level of 3,500,000 and 70 per cent respectively, and for some weeks could not be raised further despite the administration of liver extract and large doses of iron. However, on July 10, 1929, the erythrocyte count was found to be 4,490,000 and the hemoglobin, 90 per cent. The normal mean diameter of the red cells and the lack of prompt response to treatment with liver extract would place this patient's anemia definitely in the nonmegaloblastic or secondary type. In Ash-

ford's experience, this is unusual; in a recent report,[3] he stated that "in this series of anemia, sixteen cases have developed during the course of sprue; all but one of these were megaloblastic in type."

Changes in the calcium and phosphorus metabolism will be discussed in detail later in the paper.

On February 3, urinalysis did not reveal abnormalities.

Further comment should be made on the course of the thoracic condition. On January 20, there was a rise in temperature to 101 F. From this time until the condition was relieved a few days later, a septic temperature continued, reaching as high as 104.5 F. at times. On January 30, roentgenograms showed a fairly large, encapsulated accumulation of fluid in the lower right interlobar septum, and exploratory puncture was performed. Thick, yellowish-green pus containing pneumococci was obtained. On February 2, resection of a rib was performed by

TABLE 2.—*Summary of the Condition of the Blood After the Patient's Discharge*

Date	Erythrocytes, Millions per Cubic Millimeter	Hemoglobin*	Medication per Day: Liver Extract, Vial	Medication per Day: Reduced Iron, Grains	Comment
1929					
July 22	4.49	14 Gm. per 100 cc.	..	..	Doing well
Sept. 15	....	....	1	30	"Health excellent"
Dec. 10	2.77	50%	1	30	Occasional transient diarrhea
Dec. 15 (about)	3.36	60%	1	30	Occasional transient diarrhea
Dec. 18	....	....	2	30	
1930					
Jan. 3	3.68	60%	2	30	No diarrhea
Jan. 16	4.07	75%	2	30	No diarrhea
Feb. 4	4.13	65%	2	30	No diarrhea
Feb. 21	4.50	70%	2	30	No diarrhea
March 7	4.30	....	2	30	No diarrhea
March 14	4.83	....	2	30	No diarrhea
March 25 (about)	....	....	2	30	Appendectomy
April 9	4.20	....	No liver for three weeks	30	No diarrhea
May 31	4.71	85%	Amount unknown (changed to Armour's liquid liver extract)		"Feeling very well (except for numbness and tingling of fingers for 10 days); appetite very good; bowels in excellent shape; lungs not so good as I still have a marked bronchiectasis"

* The Tallquist scale was employed in determining the values for hemoglobin.

Dr. Arthur W. Allen, and on February 5, incision and drainage were carried out. Following this, daily saline irrigations of the cavity through a small rubber catheter were instituted. The cavity gradually healed, so that the drainage tube was removed on March 16.

Since discharge from the hospital, on March 20, 1929, the patient had reported by letter at frequent intervals. In general, he had done well. He had remained on a diet low in fat, moderate in carbohydrate and high in protein, with as much fruit and vegetables as possible. He had resumed the practice of medicine but had limited his activity. His medication had consisted of liver extract, and (for most of the time) 30 grains (1.95 Gm.) of reduced iron a day. He found that 1 vial of liver extract a day was insufficient, but that 2 vials were adequate to control the diarrhea. A summary of the observations on the blood is given in table 2.

3. Ashford, B. K.: The Anemias of Sprue: Their Nature and Treatment, Arch. Int. Med. **45**:647 (May) 1930.

METABOLISM STUDIES

The methods used in the metabolism ward and in the chemical laboratory were those outlined in a previous paper,[4] except that the excreta were collected in six day rather than three day periods, as had been our custom in other studies. Calcium was determined by the method of Fiske,[5] phosphorus by that of Fiske and Subbarow,[6] total base by that of Fiske[7] and total nitrogen by the macro-Kjeldahl method.[8]

Calcium and Phosphorus Metabolism.—In table 3 and figures 3 and 4 are given the data of the calcium, phosphorus and nitrogen balance and of the serum calcium and phosphorus.

One notes that this patient's diet was adequate[9] in respect to both calcium and phosphorus during period I (six days), yet the calcium and phosphorus balances were only slightly positive. The fecal values were approximately those of the intake in each instance (the intake of phosphorus was 4.48 Gm. and the fecal phosphorus, 4.07 Gm., whereas the intake of calcium was 3.72 Gm., and the fecal calcium, 3.59 Gm.). It is shown that the urinary values were extremely low, the urinary phosphorus being 0.21 and the urinary calcium 0.07 Gm. Fecal values of this magnitude must be interpreted as indicating difficulty in intestinal absorption. The low urinary values can easily be accounted for because of the existing low values for serum calcium and phosphorus. It has been well demonstrated that the serum calcium varies as the serum protein varies.[10] The lowered serum protein in this case would account for only a small part of the total reduction in the serum calcium.

The following observations enabled us to differentiate this case of tetany from one due to parathyroid deficiency: a low value for serum calcium (6.7 mg.) and serum phosphorus (1.28 mg. per hundred cubic centimeters), increased excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and decreased

4. Bauer, W., and Aub, J. C.: Studies of Inorganic Salt Metabolism: I. The Ward Routine and Methods, J. Am. Dietet. A. **3**:106 (Sept.) 1927.

5. Fiske, C. H.: Method for Calcium Determination (unpublished).

6. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375 (Dec.) 1925.

7. Fiske, C. H.: A Method for the Estimation of Total Base in Urine, J. Biol. Chem. **51**:55 (March) 1922.

8. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son and Company, 1926, pp. 711 and 713.

9. Ashford, B. K., and Hernández, L. G.: Blood-Serum Calcium in Sprue and Other Pathologic States in the Tropics, Am. J. M. Sc. **171**:575 (April) 1926.

10. Salvesen, H. A., and Linder, G. C.: Observations on the Inorganic Bases and Phosphates in Relation to the Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, J. Biol. Chem. **58**:617, 1923. Peters, J. P. and Eiserson, L.: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155 (Oct.) 1929. Albright and Bauer (footnote 2).

density of bone as determined by roentgen examination. Hypoparathyroidism, on the other hand, is characterized by: a low value for serum calcium, a high value for serum phosphorus, normal excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and normal density of bone. Therefore, the metabolism data from period I enabled us to state definitely that the tetany in this case was not due to parathyroid deficiency.

TABLE 3.—*Results of Studies of Phos*

					Phosphorus						Calcium			
					Output						Output			
Period	Date	Total Fluid Intake, Liters	Total Urine, Liters	Dried Feces, Gm.	Urine, Gm.	Feces, Gm.	Total, Gm.	Intake, Gm.	Actual Balance, Gm.	Theoretical Balance, Gm.	Urine, Gm.	Feces, Gm.	Total, Gm.	Intake, Gm.
I	1928 Dec. 5	17.7	9.5	833	0.20	4.07	4.27	4.48	+ 0.21	+ 0.51	0.07	3.59	3.66	3.72
II	11	22.6	15.2	335	0.49	1.83	2.32	7.77	+ 5.45	+ 3.80	0.38	2.51	2.89	8.39
III	17	22.8	15.1	150	0.30	6.84	7.14	15.17	+ 8.03	+ 7.20	0.44	8.54	8.98	17.34
IV	23	17.5	12.2	162	0.08	5.33	5.41	20.92	+15.51	+11.61	0.11	8.06	8.17	22.43
V	29	14.8	11.1	160	0.00	8.51	8.51	19.64	+11.13	+ 9.37	0.06	10.20	10.26	21.14
VI	1929 Jan. 4	18.3	14.9	191	0.27	8.36	8.63	23.31	+14.68	+12.44	0.05	7.92	7.97	24.41
VII	10	18.8	14.9	149	2.95	8.34	11.29	23.24	+11.95	+ 9.64	0.16	11.34	11.50	23.88
VIII	16	17.5	12.8	156	3.18	7.66	10.84	25.05	+14.21	+11.43	0.83	8.24	9.07	25.83
IX	22	15.8	12.9	251	4.90	13.22	18.12	22.34	+ 4.22	+ 5.16	1.22	17.58	18.80	23.13
X	28	11.5	6.9	156	5.32	7.14	12.46	11.61	— 0.85	+ 1.90	0.75	8.44	9.19	12.70

During period II and throughout the remainder of the study, the patient was given liver extract, 6 vials a day from periods II to V, and 3 vials a day from periods VI to X. The clinical improvement that was seen coincident with the administration of liver extract and later with the administration of large doses of inorganic iron (from periods VI to X) has already been commented on in the case report.

Parallel with this improvement in well-being, striking changes occurred in the calcium and phosphorus metabolism. With the administration of liver extract, the diarrhea improved. As a result of such improvement, the excretion of fecal calcium and phosphorus was greatly reduced (relative to the intake) and the urinary calcium and phosphorus

rose, though to a less extent (periods II and III, table 3 and figs. 3 and 4). The net result of these changes was a great retention of both calcium and phosphorus, as evidenced by total phosphorus balances of + 5.45 Gm. and + 8.03 Gm. and total calcium balances of +5.31 Gm. and + 8.36 Gm. during periods II and III, respectively. At the same time, the serum calcium rose from 6.7 to 8.2 Mg. per hundred cubic centimeters (seventh day of therapy). The serum phosphorus rose

...m and Nitrogen Metabolisms

Nitrogen				Total Caloric Intake	Blood Serum (In Mg. per 100 Cc.)				Body Weight						Treatment	
Output																
Feces, Gm.	Total, Gm.	Intake, Gm.	Balance, Gm.		Date	Calcium	Phosphorus	Total Base	Date	Kg.	Date	Red Blood Cells	White Blood Cells	Hemoglobin	Liver Extract Daily Dose, Vials	Reduced Iron per Six-Day Period, Gm.
12.4	24.6	33.0	+ 8.4	9,683	1928 Dec. 5	6.7	1.28	124	1928 Dec. 5	33.2	1928 Dec. 6	2.26	17.3	50	None	
									9	32.4						
14.2	28.5	54.4	+25.9	12,145	11	8.2	4.15	...	16	33.7		....	....	..	6	
11.1	41.5	103.5	+62.0	18,535	18	8.2	2.25	...	22	37.8		....	....	..	6	
5.6	39.6	133.8	+94.2	22,579		...	....	...	28	41.0		....	....	..	6	
5.1	48.4	129.1	+80.7	21,477	29	5.5	1.83	...		....		....	....	..	6	
10.9	66.5	158.5	+92.0	26,990	1929 Jan. 8	7.5	3.74	...	1929 Jan. 3	41.8	1929 Jan. 4	2.57	18.7	60	3	3.01
5.5	57.9	162.1	+74.2	28,371		...	....	...	10	43.8		....	....	..	3	6.14
6.5	108.2	180.3	+72.1	30,993		...	....	...	17	47.5		....	....	..	3	6.14
2.9	101.6	158.7	+57.1	28,710		...	....	...	24	49.7	23	3.36	15.9	72	3	8.19
3.2	80.2	86.2	+ 6.0	16,377		...	....	...	.	....		....	....	..	3	9.22
					Feb. 12	8.9	4.30	144	Feb. 19	45.4	Feb. 21	3.50	12.0	65		
					March 20	10.2	4.57	153	March 2	49.0	March 20	3.56	9.8	70		
									12	49.8	April 20	3.43	15.7	75		
									17	51.6	July 10	4.49	6.8	90		
									April 20	61.4						

from 1.28 to 4.15 mg. (seventh day of therapy), but had fallen to 2.25 mg. by the fourteenth day. The fall in the serum phosphorus on the fourteenth day of therapy was likely related to the marked gain in weight (4 Kg.). Much of the phosphorus retained was probably used to restore the phosphorus content of the replaced interstitial fluid as well as in the building of active protoplasm (see fixed base metabolism). That this gain in weight of 4 Kg. was due largely to the restoration of water previously lost is evidenced by the fact that the retention of nitrogen itself was not sufficient to account for the gain in weight.

In periods IV, V and VI, the previously noted increased absorption of calcium and phosphorus from the gastro-intestinal tract continued.

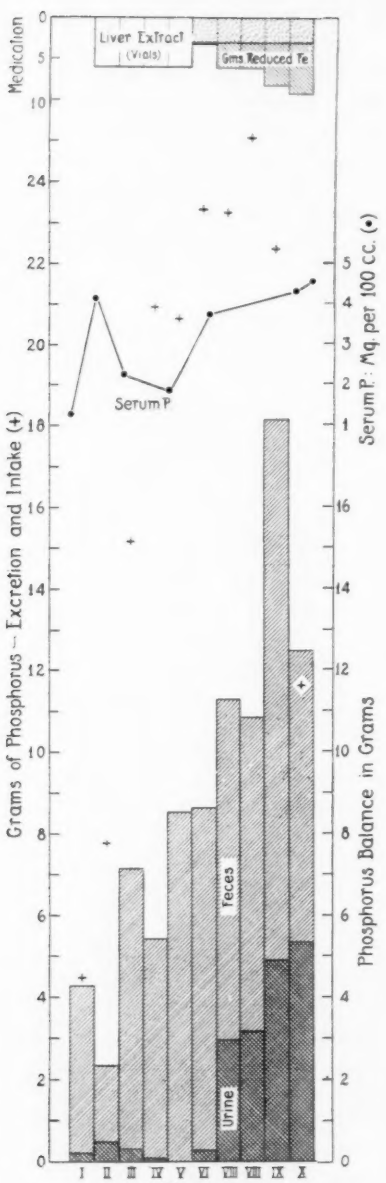
Medication
Liver Extract (Vials)
Gms Reduced Fe
Serum P
Grams of Phosphorus – Excretion and Intake (+)
Phosphorus Balance in Grams
Serum P: Mg. per 100 cc. (•)
Feces
Urine
I II III IV V VI VII VIII IX X

Figure 3

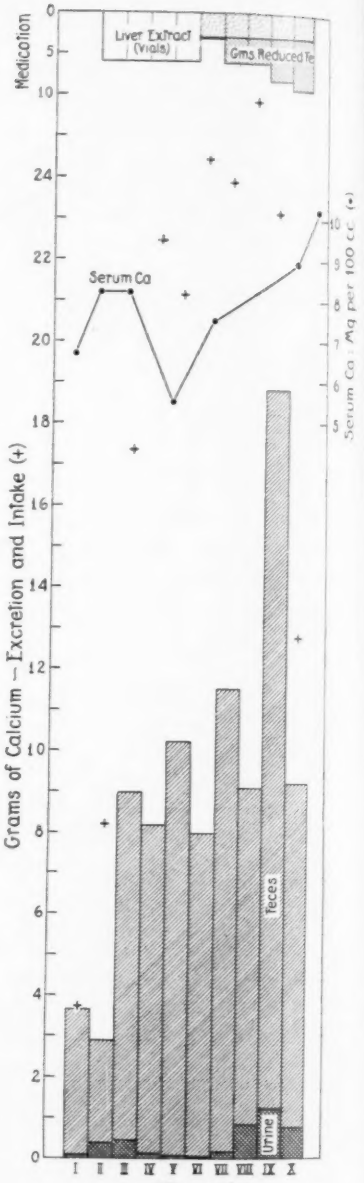
Medication
Liver Extract (Vials)
Gms Reduced Fe
Serum Ca
Grams of Calcium – Excretion and Intake (+)
Serum Ca: Mg per 100 cc. (•)
Feces
Urine
I II III IV V VI VII VIII IX X

Figure 4

Fig. 3.—Graphic representation of phosphorus metabolism, the data for which are given in table 3.

Fig. 4.—Graphic representation of calcium metabolism, the data for which are given in table 3.

However, the excretions of urinary phosphorus and calcium were much lower than they had been in periods II and III. During period V, the excretion of urinary phosphorus was so low that it could not be estimated by the method employed. During the same period, the urinary calcium was 0.060 Gm., or 10 mg. per day. Interestingly, during this period, the values for the serum calcium and phosphorus were very low (the serum calcium being 5.5 mg. and the serum phosphorus 1.83 mg. per hundred cubic centimeters). In period VI, the urinary phosphorus was increased (0.27 Gm.), but the urinary calcium remained low (0.05 Gm.), approximately 8 mg. a day. However, the serum calcium increased to 7.5 mg., and the serum phosphorus to 3.74 mg. Despite these low values for the urine and serum, a large amount of calcium and phosphorus was retained during periods IV, V and VI. For example, during period VI, the balance of phosphorus was positive to the extent of 14.68 Gm. and the balance of calcium to the extent of 16.4 Gm.

In period V, the low value for serum calcium and the further reduction of the serum phosphorus were probably the result of the deposition of calcium and phosphorus in bone and the establishment of the normal concentration of these substances in the interstitial fluid. Once the latter was accomplished, the increased retention of calcium and phosphorus was reflected in the blood, with elevation of both the serum calcium and phosphorus (period VI, during which the serum calcium was 7.5 mg. and the serum phosphorus was 3.75 mg. per hundred cubic centimeters).

Period VIII represents an advance toward the normal state, with continued high calcium and phosphorus balances. In period IX, there was an increase in the fecal calcium and phosphorus; this is accounted for by an increase in the intestinal rate (note the increase in the weight of the feces, table 3). This was present to some extent in period X, as is shown by the high excretion of fecal calcium and phosphorus (relative to the intake). The gradually increased excretion of urinary phosphorus and decreasing positive nitrogen balance were the result of the increased destruction of protein associated with the interlobar empyema and hyperpyrexia. The loss of weight during this period is further evidence of the increased destruction of protein.

Metabolism of Fixed Base.—On the first day of period I, the serum total base was found to be 124 mg. per hundred cubic centimeters (this determination was done in duplicate, and the two results checked extremely well). We believe that this is as low a serum total base as has ever been reported. This value for serum total base was consistent with the severe dehydration present on the patient's entrance to the

hospital. Other workers [11] have adequately demonstrated that severe dehydration associated with diarrhea is due to a loss of water and electrolytes from the intercellular fluid. This loss of water and electrolytes is not reflected in the blood plasma until the intercellular fluid has been almost depleted. If the diarrhea continues sufficiently long, an actual reduction in the plasma electrolytes results and the volume of plasma may be reduced one-third. (Detailed studies of this nature were not undertaken because the patient was so acutely ill.) It is interesting that with the improvement of the diarrhea a rapid gain in weight resulted. This gain in weight during periods II to VI was far greater than could ever be accounted for by the increased positive nitrogen balance. It must therefore be interpreted as due to the replacement of the water and electrolytes of the plasma and intercellular fluid. This replacement was secondary to the more complete absorption and

TABLE 4.—*Comparison of Actual and Calculated Phosphorus Balances*

	Phosphorus Balances			
Period	Theoretical, Calculated from Calcium Balance, Gm.	Theoretical, Calculated from Nitrogen Balance, Gm.	Total Theoretical Balance, Gm.	Actual, Gm.
I	0.026	0.48	+ 0.51	+ 0.21
II	2.310	1.49	+ 3.80	+ 5.45
III	3.630	3.57	+ 7.20	+ 8.03
IV	6.200	5.41	+11.61	+15.51
V	4.730	4.64	+ 9.37	+11.13
VI	7.150	5.29	+12.44	+14.68
VII	5.380	4.26	+ 9.64	+11.95
VIII	7.290	4.14	+11.43	+14.21
IX	1.880	3.28	+ 5.16	+ 4.22
X	1.550	0.35	+ 1.90	— 0.85

the decreased excretion which followed the restoration of a normal intestinal rate. With these resultant changes, the serum total base gradually approached normal.

Comparison of the Actual and Calculated Phosphorus Balances.—In table 4 the data on the phosphorus balances are presented in a form which makes possible the comparison of the "theoretical" or calculated phosphorus balance with the actual or determined phosphorus balance. The method employed in making such calculations has previously been reported.[12]

The results show that the actual and calculated phosphorus balance in period I agree very well. From here on one notes that less phosphorus

11. Hartman, A. F.: Chemical Changes Occurring in the Body as the Result of Certain Diseases, Am. J. Dis. Child. **35**:557 (April) 1928. Salvesen and Linder (footnote 10, first reference).

12. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: IV. The Effect of the Parathyroid Hormone, J. Clin. Investigation **7**:139 (April) 1929.

is excreted than was expected according to the calculated phosphorus balance. These differences can probably be accounted for by the replacement of interstitial fluid substances. In period IX, the increased intestinal rate resulted in a greater excretion of phosphorus than would have been expected from the calculated balance. The period X, the actual phosphorus balance was negative, whereas the theoretical phosphorus balance was positive. This difference was due to the increased destruction of protein.

Nitrogen Metabolism.—Period I (table 3) shows that nitrogen balance was barely present, (+ 8.4 Gm.) before therapy was started. Subsequent to the improvement in the diarrhea, the positive nitrogen balances increased, reaching + 94.2 Gm. in period IV. With a tendency of the diarrhea to return, added to the increased destruction of protein, the positive nitrogen balance decreased, so that in period X it was only + 6.2 Gm.

COMMENT

A consideration of the symptoms, clinical course and laboratory studies as outlined leaves little doubt as to the correctness of the diagnosis. The history of recurring attacks of diarrhea, sore tongue, anemia, extreme cachexia and irritability, together with the large, bulky, watery, foamy, light-colored stools, possessing a characteristic yeasty odor, is in accord with the clinical picture of sprue, even though the patient had always lived in the northern part of the United States. It is somewhat difficult to formulate possible causative factors in this case, although the patient's present unusual dietary whims suggest a probably unbalanced and deficient diet in the past. His developmental state suggests that constitutionally his resistance to any chronic disease had probably always been low.

Although in most reports tetany is not stressed as a complication of sprue, a review of the literature reveals a number of such cases. Frequently, note is made of the occurrence of cramps in the extremities; some of these reports undoubtedly represent instances of tetany, although unrecognized as such by the examiner. In 1913, Cantlie [13] mentioned having seen six cases of tetany with generalized spasms and marked anemia in patients with sprue of long duration. He considered that "these attacks do not imply a fatal issue to the malady." He did not, however, report values for blood calcium. Harrison [14] saw one case of sprue with marked tetany. In 1919, Bassett-Smith [15] reported

13. Cantlie, J.: Some Recent Observations on Sprue, Brit. M. J. **2**:196 (Nov. 15) 1913.

14. Harrison, W. S., in discussion on Cantlie, Brit. M. J. **2**:1296, 1913.

15. Bassett-Smith, P. W.: A Case of Sprue Associated with Tetany, Lancet **1**:178 (Feb. 1) 1919.

a case of tropical sprue complicated by tetany in the terminal stage of the disease. Values for blood calcium were not recorded. Bovaird [16] reported two cases of sprue with tetany, one of which had been described by Barach and Murray.[17] One of Bovaird's patients had a serum calcium which varied from 6.5 to 8 mg. per hundred cubic centimeters; the other had values from 6.6 to 7 mg.

In 1923, Blumgart [18] reported three fatal adult cases in which there was gradual progressive weakness and emaciation over a period of months, with loose, fatty, bowel movements, achlorhydria and anemia. Two of the three cases exhibited tetany, and in one values for serum calcium of 5.3 mg. and for phosphorus of 2.6 mg. per hundred cubic centimeters were recorded. In all three cases, postmortem examination showed collections of fat-laden phagocytes in the mesenteric lymph nodes and the mucosa of the small intestine. Blumgart did not regard his cases as characteristic of sprue.

In 1923, Scott [19] reported tetany in a case of sprue and mentioned having seen this complication in many other cases. He observed improvement in such cases with the use of calcium lactate and parathyroid extract by mouth and believed that parathyroid deficiency was intimately concerned with the lowered values for serum calcium and the tetany. All figures for "total" serum calcium quoted in Scott's paper, however, are normal values; his distinction between free and combined calcium is not justified in the light of present knowledge.

One of Jamieson's [20] patients had tetany, as did the one in Thaysen's [21] series, case 8. Neither observer reported values for serum calcium.

In 1926, in Porto Rico, Ashford and Hernández [9] reported the results of a study of the serum calcium in sprue and in other chronic diseases. In one group of twenty-eight cases, they found values ranging from 7.2 to 10.8 mg., with fifteen instances of a value below 9 mg. (the average value given by them for normal healthy controls was 9.6 mg. per hundred cubic centimeters). However, critical study of their figures

16. Bovaird, D.: A Study of Tropical Sprue, or Psilosis, J. A. M. A. **77**:753 (Sept. 3) 1921.

17. Barach, A. L., and Murray, H. A., Jr.: Tetany in a Case of Sprue, J. A. M. A. **74**:786 (March 20) 1920.

18. Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat: With Emaciation and Anemia, and in Two Acidosis and Tetany, Arch. Int. Med. **32**:113 (July) 1923.

19. Scott, H. H.: The Nature and Treatment of Sprue, Brit. M. J. **2**:1135 (Dec. 15) 1923.

20. Jamieson, T. H.: The Treatment of Sprue, Brit. M. J. **2**:462 (Sept. 15) 1923.

21. Thaysen, T. E. H.: Ueber Fettdiarrhöen: III. Die Klinik der nichttropischen Sprue, Acta med. Scandinav. **64**:352 (Sept.) 1926.

reveals that little correlation existed between the clinical severity of the disease and the level of the serum calcium. Indeed, in one series of fifty-five cases, five of the eight "mild" cases and four of the six "moderately severe" cases had values for serum calcium below 9 mg., while only seven of the twenty-one "severe" cases and only nine of the nineteen cases with cachexia had values for calcium below 9 mg. Further, they found that low values for serum calcium were obtained in conditions of malnutrition other than sprue (mention is not made of the concentration of the serum protein [10]). Determinations of the serum phosphorus were not made in any of their cases. They, as well as Scott,[19] questioned whether or not in sprue or in the other conditions studied parathyroid deficiency might be considered as the basis of the low values obtained.

Baumgartner and Smith,[22] in a study of fifteen cases of sprue, found eight patients with values for serum calcium below 9 mg. per hundred cubic centimenters; three of them showed positive Chvostek and Trousseau signs.

More recently, Holmes and Starr [23] reported a series of five cases in which the clinical course bore a striking similarity to the one outlined in this paper. All of their patients had low values for serum calcium, and at one time or another four of the five had active tetany. The authors obtained great improvement with the administration of calcium lactate and Collip's parathyroid extract.

A rise in the serum calcium and relief from tetany were experienced by our patient when Collip's parathormone was administered. However, the fact that tetany associated with sprue is benefited by the administration of an active parathyroid extract is anything but proof that either the sprue or the tetany is related to parathyroid deficiency. The elevation of the serum calcium following the administration of a potent parathyroid extract is due to the ability of this agent to mobilize calcium and phosphorus from bone. This indicates that parathyroid extract should be used only as a temporary expedient to alleviate the tetany. Diarrhea is not a symptom of parathyroid deficiency. Parathyroid deficiency, as has been stated before, is characterized by: a low value for serum calcium, a high value for serum phosphorus, normal excretion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and normal density of bone. Cases of tetany such as the one reported are characterized by a low value for serum calcium, a low value for serum phosphorus, increased excre-

22. Baumgartner, E. A., and Smith, G. D.: Pernicious Anemia and Tropical Sprue, Arch. Int. Med. **40**:203 (Aug.) 1927.

23. Holmes, W. H., and Starr, P.: A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue: Emaciation, Anemia, Tetany, Chronic Diarrhea and Malabsorption of Fat, J. A. M. A. **92**:975 (March 23) 1929.

tion of fecal calcium and phosphorus, decreased excretion of urinary calcium and phosphorus and decreased density of bone. Tetany is a syndrome and not a disease entity. Its causes are many. Parathyroid deficiency is only one of the many conditions that produce tetany. Any condition that hinders the absorption of calcium and phosphorus from the gastro-intestinal tract in the amounts necessary to meet the requirements of the body might eventually result in tetany. Some of these conditions are: (1) dietary insufficiency of either calcium or phosphorus,[24] (2) deficiency in vitamin D,[25] (3) diets containing a great excess of calcium over phosphorus, or vice versa,[26] (4) long-standing diarrhea,[27] (5) any disease hindering absorption from the gastro-intestinal tract,[28] (6) long-standing biliary or intestinal fistulas[29] and (7) excessive excretion of fat.[30]

If any of these conditions persisted, the patient would eventually suffer from deficiency in calcium. If the deficiency in calcium remained uncorrected, tetany would ultimately develop. The calcium and phosphorus stored in the bone would suffice for the needs of the body for a time, thus preventing the earlier onset of tetany.

The patient in the case reported had suffered from diarrhea for three years, and intermittently during the preceding five years. He had

24. Maxwell, J. P.: Osteomalacia in China, J. Obst. & Gynæc. Brit. Emp. **32**:1, 1925. Hess, A. F., and Lewis, J. M.: Clinical Experience with Irradiated Ergosterol, J. A. M. A. **91**:783 (Sept. 15) 1928. Hess, A. F.: Rickets Including Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929.

25. Steenbock H., and Nelson, M. T.: Fat-Soluble Vitamins: XIX. Induction of Calcifying Properties in a Rickets-Producing Ration by Radiant Energy, J. Biol. Chem. **62**:209, 1924. Hess and Lewis (footnote 24, second reference).

26. Karelitz, S., and Shohl, A. T.: Rickets in Rats: II. The Effect of Phosphate Added to the Diet of Ricketic Rats, J. Biol. Chem. **73**:665 (June) 1927. Orr, W. J.; Holt, L. E., Jr.; Wilkins, L., and Boone, F. H.: The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine, Am. J. Dis. Child. **28**:574 (Nov.) 1924.

27. Linder, G. C., and Harris, C. F.: Calcium and Phosphorus Metabolism in Chronic Diarrhea with Tetany, Quart. J. Med. **23**:195 (Jan.) 1930.

28. Parsons, L. G.: Bone Changes in Renal and Celiac Infantilism, Arch. Dis. Child. **2**:1 (Feb.) and 198 (Aug.) 1927.

29. Tammann, H.: Ueber die Beeinflüssung der porotischen Osteomalazie nach Gallenfistel durch das D-Vitamin, Beitr. z. klin. Chir. **142**:83, 1928. Dieterich, H.: Die porotische Malazie nach Gallenfisteln, Beitr. z. klin. Chir. **134**:530, 1925. Seifert, E.: Zur Frage der porotischen Malazie nach Gallenfisteln, Beitr. z. klin. Chir. **136**:496, 1926. Düttmann, G.: Die Veränderung des Säure-Basengleichgewichtes nach Gallenfisteln und ihre Bedeutung bei der Entstehung der sogenannten porotischen Malazie, Beitr. z. klin. Chir. **139**:720, 1927.

30. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism: IV. The Influence of Free Fatty Acids in the Intestine on the Absorption and Excretion of the Mineral Elements, Quart. J. Med. **20**:1, 1926; V. Infantile Rickets: The Excretion and Absorption of the Mineral Elements and the Influence of Fats in the Diet on Mineral Absorption, ibid., p. 7.

achlorhydria and a complete absence of lipolytic enzyme activity. Both of these abnormalities are known to cause diarrhea. Achlorhydria and decreased pancreatic enzyme activity are not uncommon in sprue.[31] Besides the diarrhea in this case, there are two other factors that might conceivably interfere with the absorption of calcium and phosphorus, namely, achlorhydria and the absence of lipolytic enzyme activity. The effect of the achlorhydria on the absorption of calcium and phosphorus cannot be stated with any degree of certainty, but it is generally accepted that lowered intestinal acidity hinders such absorption.[32] The increased excretion of fat (due to the absence of lipolytic enzyme activity) has been shown to result in the formation of insoluble calcium soaps, which are subsequently excreted.

The facts that the excretion of fecal calcium and phosphorus almost equalled the intake of these substances and that these fecal values decreased following the improvement of the diarrhea would seem sufficient evidence that the tetany in this case resulted from faulty absorption secondary to the diarrhea. Various workers have demonstrated that sprue, like pernicious anemia, is also a deficiency disease.[33]

It would be interesting to speculate as to what effect a concentrated preparation of vitamin D would have had on this patient. However, if his condition was in any way related to a deficiency in vitamin D, this lack was not corrected materially by the administration of liver extract because the content of vitamin D in such preparations is extremely low. Presumably, an increased absorption of vitamin D might have resulted in the improvement of the diarrhea.

SUMMARY

1. Studies of the calcium and phosphorus metabolism in a case of nontropical sprue with associated tetany are reported.

2. It is emphasized that the low serum calcium and phosphorus, the osteoporosis and the tetany seen in cases of sprue are not the result of parathyroid deficiency, but are due to the inadequate absorption of

31. Sokhey, S. S., and Malandkar, M. A.: Pancreatic Function in Sprue, Indian J. M. Research, **25**:921 (April) 1928. (See this article for additional references.)

32. Irving, L., and Ferguson, J.: The Influence of Acidity in the Intestine Upon the Absorption of Calcium Salts by the Blood, Proc. Soc. Exper. Biol. & Med. **22**:527 (May) 1925. Babbott, F. L., Jr.; Johnston, J. A., and Haskins, C. H.: Gastric Acidity in Infantile Tetany, Am. J. Dis. Child. **26**:486 (Nov.) 1923.

33. Porter, W. B., and Rucker, J. E.: The Treatment of Non-Tropical Sprue with Liver Extract, Am. J. M. Sc. **179**:310 (March) 1930. Elders, C.: Behandlung der Tropischen Sprue, Med. Welt **3**:167, 1929.

calcium and phospohrus from the gastro-intestinal tract because of the existing diarrhea.

3. In the case reported, improvement took place coincident with the giving of 6 vials of liver extract daily. Subsequently, 2 vials a day were found to be sufficient.

4. A very low value for serum total base (124 mg. per hundred cubic centimeters) is reported.

Book Reviews

THE RENAL LESION IN BRIGHT'S DISEASE. By THOMAS ADDIS and JEAN OLIVER. Price, $16. Pp. 650, with 160 full page illustrations and 21 text illustrations. New York: Paul B. Hoeber, Inc., 1931.

In this modern day of haste, with its attending evil, superficiality, the survey of a book such as that of Addis and Oliver affords unusual pleasure. Unusual not only because of its thoroughness, a thoroughness that carries the conviction of authority, but because the presentation is as forceful as it is personal, and the subject matter so logically and clearly studied and developed, that there is never any doubt in the mind of the reader that the objectives of the authors have been unquestionably achieved. To call it a landmark were trite. To say that it reflects genuine credit on American medicine is but fair appreciation of the enormous labor, the careful observation and the keen analysis that have been condensed in the volume.

It differs from many other works dealing with the subject because of its absolute objectivity. It is built on bed rock. And even to those who may stray from the narrow pathway of the microscope into the wider, though less certain, thoroughfares of pathologic physiology, the very solid pathologic basis is as refreshing as it is convincing. So, too, the clinical observations are based not only on thorough study, but on urinalyses that are unique in their approach to quantitative exactitude—methods that have been under development by Addis for many years. The reviewer would like, in passing, to emphasize their value, as they are not sufficiently known to the medical profession at large. Addis has not only worked out the quantitative analysis of the urinary sediment and reasonably satisfactory measures of the maximum functional capacity of the renal tissue, in themselves of enormous clinical value, but has made such functional determinations over long periods of time. Only by such long-continued functional surveys can a true picture of the clinical condition be obtained. His insistence that the clinician himself should examine the sediment strikes a responsive cord. Too much routine work is delegated to technicians. Chemical determinations are justifiable; examination of the urinary sediment, with care for its proper collection, should be done by the physician himself. The authors make it very evident that the urine so examined offers a store of information about the patient to the careful examiner. Were there nothing else of value, the first four chapters (I. Introduction; II. Clinical Methods; III. Clinical Definitions; IV. A Clinical Classification of Bright's Disease in Accordance with the Nature of the Renal Lesion) would in themselves justify the book.

Oliver made a pathologic study of the seventy-two cases of Bright's disease that form the basis of the work. Each case is discussed in detail: the history, the clinical picture, the salient gross pathologic changes and the description of the microscopic examination. The 160 plates (magnified 20 and 120 times) represent photomicrographs that are in themselves instructive as well as technically excellent. The reviewer has been particularly impressed with the descriptive terseness, all nonessential detail having been omitted, which in itself is convincing evidence of the sense of proportion that is conveyed by the entire book.

To illustrate finer details that are essential in the analysis presented in the final chapters (VI. Pathological Definitions; VII. The Clinical and Pathological Observations; VIII. Clinical Summary and Comparison of Clinical and Pathological Data; IX. A Correlation of the Clinical and Pathological Observations; X. A Theoretical Description of the Course and Sequence of the Pathological Processes in Bright's Disease; XI. A Classification and Theory of Bright's Disease), Feinberg has made a series of drawings of high power fields. Their quality is in keeping with the rest of the book in which typography, binding, form and paper are of exceptionally high standard.

The reviewer has called attention to the mature balance that pervades the book, and to its objectivity. It has not been the purpose of the authors to spread—limitation has permitted depth. There has been no attempt, for instance, to discuss hemorrhagic Bright's disease from the point of view of general capillary damage. The focus is on the kidney, and is clearly so stated in the title. This limitation in no wise lessens the value of the book to the clinician or to the scientific investigator.

Addis and Oliver have contributed a book that should be of enormous value to every clinician; stimulating, intensely practical and thoroughly readable and understandable as books are apt to be when the authors are masters of their subject.

NOGUCHI. By GUSTAV ECKSTEIN. Price, $5. Pp. 419. New York: Harper & Brothers, 1931.

Three years after Hideyo Noguchi, a famous Japanese bacteriologist, lost his life in Africa through his untiring search for the organism responsible for yellow fever, the general reading public is made acquainted with the facts of his life through this biography by Gustav Eckstein. This volume ought to prove interesting to the members of the medical profession whether they knew Noguchi personally or are familiar with his work. However, the lack of technical language and the lucid explanations of all experimental procedures indicate that the author intended to bring the book to the attention of the layman as well as to that of the physician.

If one can overlook marked deficiencies in the literary style and an all too frequent repetition of irrelevant detail, one will be able to gain a good deal of pleasure from this account of Noguchi's colorful career and his valuable contributions to the study of organisms responsible for disease. The numerous facts that the author brings to bear on each period of Noguchi's life, from his very humble boyhood to his sad death, indicate that he had access to a vast number of letters written by, to and about Noguchi, as well as an insight into the circumstances of his life. One feels that if the author had exercised greater discrimination in his choice of material, he could have written a much finer book. He presents so many facts that he is unable to give proper emphasis to the really important things.

However, whatever faults may be noted in regard to technical qualities, it is apparent that Mr. Eckstein has painted a convincing word portrait of a remarkable personality. Noguchi's accomplishments are secondary to his character, and whenever a description of a unit of his work occurs, it serves to illustrate some trait or traits in his character. Although the work that he executed marked him as a "genius," he is, nevertheless, as one examines his reflection in this book essentially a "man"—happy and proud when he succeeded in something he set out to do; discouraged and despondent when he failed; sensitive to criticism, and appreciative of courtesies shown him.

In order that the reader may understand something of the interest that lies in this book, certain bents of personality will be illustrated by quotations from it. Time after time the author describes the intensity with which Noguchi applied himself to his work: "He was in the laboratory through the whole of last night, through the whole of yesterday, through the whole of the night before." One marvels at the manner in which his will was able to dominate bodily weaknesses. That he was able to live to the age of 51, in spite of his devotion to labor and a body weakened by disease, is nothing short of miraculous. Rather humorous are the anecdotes dealing with his lack of understanding of business matters and the resultant lack of funds: "As to science I am a great success but as to financial conditions I am below zero point." There is something pathetic in his effort to hide the deformed left hand which had been so severely burned when he was a boy: "He has learned to hide his hand. . . . He drops his cap over it, or folds his arms in front of him slipping the left hand under the elbow." When triumph comes to him, he says, "I am the first to cultivate the spirochete of

syphilis. . . . In Copenhagen they gave me the Royal Medal. . . . It is said that the Swedish crown intends to decorate me. . . . I have sat with great men of science and become intimate with them." His elation at success is no more marked than his despondency at failure: "I feel only the smallness and weakness of man." His understanding of genius corresponds with that of some psychologists: "There is no such thing as genius. . . . It is hard work. That is genius."

These are but a few angles of the character which Mr. Eckstein stresses. Noguchi's name has gone down in medical history because of his work and the methods he employed, and now the facts of the life that lay back of these accomplishments will go on record and thus be saved from oblivion. Those of the medical profession who value personal qualities in their colleagues and predecessors cannot help but be inspired by the life story of this great little Nipponese who, through his work in America, received the recognition of the highest scientific orders throughout the world.

THE PHYSICIAN OF THE DANCE OF DEATH. By ALDRED SCOTT WARTHIN. Price, $7.50. Pp. 142, with 92 illustrations. New York: Paul B. Hoeber, Inc., 1931.

The Dance of Death in art and literature is an expression of the common conception of death as a leveler and conqueror of all. The conception is doubtless as old as the time that man first began to philosophize about his existence and his end, but its expression in art began in the Middle Ages, and was most frequent in that morbid period. As Warthin says, "The most satisfactory explanation of the origin of the Toten Tanz motive is to be found in the psychology of the times, which constantly stressed the thought of death and the vanity of all earthly things." "It was a neurotic and psychopathic age, as shown in its superstitions, its religious fanaticism, its sensuality, belief in witchcraft and magic." But the idea has never since failed to interest artists when in their contemplative moods, and it is still used by them even down to pictures of the last Great War. Of course expression of the idea varies with the varying mental attitude of succeeding centuries, but the essential theme is the same.

The study of the subject became a hobby of Warthin's in his professional youth. "In 1893, a young medical student on his way to Vienna passed through Nuremburg. In a shop window, in the street leading up to the castle, a print caught his eye. It was Albrecht Durer's 'Ritter, Tod und Teufel.' So deep was the impression made by it upon the susceptible, perhaps somewhat sentimental, youth, that the print at once became his own; and the brave Knight, who feared neither Death nor Devil, came to represent to him an ideal of life." The ideal became in Warthin a fine one, to fear neither death nor devil and to love truth.

From that time Warthin began to collect illustrations of the Dance of Death, and this volume is a result of that hobby. A great number of illustrations are reproduced, nearly all from copies or originals in his collection. The volume ends with a bibliography of the Dance of Death in Dr. Warthin's collection, and in addition a bibliography of the short list not in his collection. It makes a fascinating book, both in text and in illustrations. One can spend, not an interesting hour, but interesting hours analyzing the various ways the theme is illustrated in the many cartoons. Warthin has made this exercise easier by his text.

This diversion was one out of which he evidently got much interest. As he says, "He can wish his colleagues no greater pleasure than the pursuit of such a hobby." It is a fine illustration of the pleasure of a hobby, something the reviewer agrees with Warthin that every man should develop early in his career for his own satisfaction. One will be better for it, if it is a hobby of cultural interest, as it was with Warthin, and if it is a hobby that involves some aspect of one's own philosophy of life. The latter was evidently true in Warthin's case. His vocation emphasized death as an item of his philosophy, and this hobby, perhaps, was a result. But it was not a neurotic or a morbid interest; it was a frank

acceptance of death as a normal physiologic end, and Warthin's was the same attitude of quiet courage of the well known lines of Shakespeare with which Warthin ends his book:

> "It seems most strange that men should fear;
> Seeing that Death, a necessary end,
> Will come when it will come."

This handsome book has two good reasons for being on the shelves of physicians: (1) the interest of the book itself and (2) as a reminder of a successful diversion for a physician of culture.

The publisher deserves a word of praise; the book is a fine example of the printer's art.

RADIUMTHERAPIE, METHODEN UND AUSSICHTEN. By DR. F. GUDZENT, a. ö. Professor an der Universität Berlin. Band V. Medizinische Praxis, Herausgegeben von Grote, Fromme, Warnekros. Paper. Price, 6.50 marks. Pp. 116, with 53 illustrations. Leipzig: Theodor Steinkopff, 1929.

The booklet serves as a short, concise handbook of reference regarding the indications and usage of radium in medicine. A short résumé of the discovery of radium and of its physical and chemical properties is given. The decay of radium and its emanation are explained, and filtration principles with various types of radium applicators are illustrated and explained.

The biologic response of skin, muscle, tendon, cartilage, bone, nervous tissue and the blood to the action of the rays from radium is reported.

Indications and technic of treatment in gout, rheumatism, neuritis, blood dyscrasias and chronic suppuration by inhalations of emanation and by drinking and bathing in radio-active waters are given, and the radium content of the waters of various popular German watering places is included.

Types of lesions of the skin amenable to the action of radium are briefly discussed; for deeper tumors, the importance of combined surgery and radium usage is stressed. The gynecologic uses of radium are fully entered into.

THERAPIE DER ERKRANKUNGEN DES VEGETATIVEN NERVENSYSTEMS. Price, 7 marks. P. 96. Dresden: Theodor Steinkopff. German Society for the Advancement of Medicine, 1930.

This book contains a series of lectures given at Bad Oeynhausen by various specialists. The vegetative nervous system is discussed from various points of view in an extremely elementary manner, so that not even a complete survey of the subject may be obtained.

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